Sex, Estrogen and Working Memory: The Effects of Sex-Related Differences and Estrogen Suppression on Neuropsychological Test Performance

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Abstract

This body of research investigates the effects of sex and estrogen on higher brain functions, in general, and on working memory, in particular. A female advantage for object-location and verbal working memory has been reported, and estrogen supplementation facilitates performance of the same. Less is known about whether the female advantage is due to the verbalizability of the stimuli, and whether estrogen-suppression adversely affects performance on working memory and other neuropsychological domains sensitive to estrogen. Study 1 examined sex-related differences in young adults on an object-location working memory measure that varied in verbalizability of stimuli and task presentation (i.e., manual or computer); as expected, females performed better than males regardless of the verbalizability of the stimuli or task presentation. Study 2 examined sex-related differences in young adults on the n-back working memory task across verbal, spatial, and object conditions. Contrary to the hypotheses, there was no sex effect for the verbal version of the n-back task, and males actually performed better than females on the object version; as expected, males performed better than females on the spatial version. Study 3 investigated the effect of estrogen suppression in middle-aged and older adult females undergoing treatment for estrogenic breast cancer using the experimental working memory measures from Studies 1 and 2, and a comprehensive neuropsychological battery that included measures considered to be either sensitive (e.g., letter fluency) or insensitive (e.g., spatial ability) to the female advantage and the effects of estrogen. The estrogen suppression group performed more poorly than healthy age-matched controls on certain estrogen-sensitive measures (i.e., speeded visuomotor attention, speeded manual dexterity, and letter fluency), but unexpectedly, the groups did not differ on any of the memory measures presumed to be estrogen-sensitive. This body of research suggests that although certain working memory measures are sensitive to sex effects, the direction depends on the domain, and that estrogen suppression does

not impact working memory in postmenopausal women but does adversely impact speeded performance measures.

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General Introduction

This body of research examines the effect of sex and estrogen suppression on working memory. Sex-related differences in the human central nervous system are observed morphologically, physiologically, and functionally; for example, females and males differ with regard to the size of various cortical areas or structures (e.g., Giedd et al., 1996; Gur, Gunning-Dixon, Bilker & Gur, 2002; Schlaepfer, Harris, Tien, Peng, Lee & Pearlson, 1995), sex steroid hormone receptor sites (Bixo, Backstrom, Winblad & Anderson, 1995; Goldstein et al., 2001; McEwan & Alves, 1999; Sholl & Kim, 1989; Shughrue & Merchenthaler, 2000), and neuropsychological performance (e.g., Bryden & Roy, 2005; Crossley, D'Arcy & Rawson, 1997; Duff & Hampson, 2001; Speck, Speck, Ernst, Braun, Koch, Miller & Chang, 2000; Sykes-Tottenham, Saucier, Elias, & Gutwin, 2005). Specifically, the prefrontal cortex, which subserves the neuropsychological function of working memory (e.g., Becker, MacAndrew & Fiez, 1999; D'Esposito, Postle, Ballard & Lease, 1999; Fuster, 1973) is larger in volume in females compared to males (Goldstein et al., 2001; Schlaepfer et al., 1995), and is rich in estrogen receptors compared to other cortical areas (Bixo, Backstrom, Winblad & Anderson, 1995; McEwan & Alves, 1999; Sholl & Kim, 1989; Shughrue & Merchenthaler, 2000). It follows that a female advantage for object-location and verbal working memory has been observed (Duff & Hampson; Speck et al., 2000), and that estrogen supplementation has been shown to facilitate performance on these measures (Hampson & Duff, 2000; Keenan, Ezzat, Ginsburg & Moore, 2001). Less is known, however, about sex differences on working memory measures that are considered to be relatively nonverbal (e.g., non-verbalizable stimuli, spatial working memory), or the effect of estrogen suppression on working memory in middle-aged and older females.

The research described in this dissertation investigates sex-related differences in verbal and nonverbal working memory domains, and the effect of estrogen suppression on working

memory and other neuropsychological functions. The first experiment examines sex-related differences on an object-location working memory measure in healthy young adults; the degree of verbalizability of the stimuli and mode of presentation (i.e., manual versus computer task) were manipulated. The second experiment examines sex-related differences in healthy young adults using verbal, spatial and object versions of the "n-back" working memory measure. Finally, the third experiment examines the effect of estrogen suppression in middle-aged and older females undergoing treatment for estrogenic breast cancer using the experimental working memory measures from the first and second experiments, and a comprehensive neuropsychological battery of tasks that includes tasks presumed to be either sensitive (e.g., verbal memory) or insensitive (e.g., spatial ability) to estrogen levels.

Sex and the Central Nervous System

Sex-related differences in the mammalian central nervous system have been known for several decades (e.g., Gorski, Harlan, Jacobson, Shryne & Southam, 1980; Raisman & Field, 1971). There are several sex-related differences in the gross morphology of the adult human central nervous system. Autopsy and structural magnetic resonance imaging (MRI) studies have shown that compared to females, males have overall higher cerebral volume (Gur et al., 2002; Filipek, Richelme, Kennedy, & Caviness, 1994; Witleson, Glezer, & Kigar, 1995), white matter volume, and cerebral spinal fluid volume (Gur et al., 1999). In contrast, females have higher grey matter volume compared to males (Gur et al., 1999), although this finding is inconsistent (e.g., Resnick et al., 2000). Sex-related differences in adult regional cortical morphology are also reported. Perhaps the largest and most robust finding in postmortem studies is the significantly larger preoptic area of the hypothalamus, involved in reproductive behavior, in males compared to females (Allen, Hines, Shryne, & Gorski, 1989; Swaab & Fliers, 1985). Sex-related differences favouring females have also been observed for the corpus callosum (e.g., DeLacoste-

Utamsing & Holloway, 1982), but these differences have been tempered by region (Dubb, Gur, Avants & Gee, 2003) or disputed altogether (e.g., Allen, Richey, Chai & Gorski, 1991; Leonard et al., 2008). On MRI, males have more grey matter in the medial frontal lobes, angular gyrus of the parietal lobes, amygdala, and hypothalamus (Goldstein et al., 2001; Frederikse, Lu, Aylward, Barta, & Pearlson, 1999), typically associated with arousal and motivation, spatial processing, emotional regulation, and sexual behavior, respectively. In contrast, females have larger Broca's area (Harasty, Double, Halliday, Kril, & McRitchie, 1997), superior temporal gyrus, including the planum temporale (Harasty et al., 1997; Schlaepfer et al., 1995), hippocampal regions (Giedd et al., 1996; Goldstein et al., 2001), orbital prefrontal cortex (PFC) (Gur et al., 2002; Goldstein et al., 2001), and dorsolateral PFC (Goldstein et al., 2001; Schlaepfer et al., 1995). These identified regions are typically associated with language expression, language reception, memory processing, emotional and social behavior, and working memory, respectively.

The sexual dimorphism found in the human central nervous system is hypothesized to be at least partly attributable to the mechanism of sex steroid hormones. For example, the preoptic area of the hypothalamus has a relatively high number of androgen receptors, which likely contributes to the larger size of this area in males as compared to females (Kruijver, Fernandez-Guasti, Fodor, Kraan, & Swaab, 2001). In this vein, Goldstein et al. (2001) hypothesized that the regions of the cortex that were sexually differentiated would also be the most sensitive to the effects of sex hormones, as correlated with the number of sex hormone receptors in the area. The cortical differences found between males and females roughly correspond to the distribution of estrogen receptors in females and androgen receptors in males; females had higher volumes of orbital, superior, precentral, and lingual cortex compared to males, which are all areas associated with high levels of estrogen receptors.

Sex-related differences in the morphology of the human central nervous system are found to interact with age. Overall, postmortem and structural MRI studies show that total grey matter volume decreases and cerebrospinal fluid increases in both sexes with age (Gur, Gunning-Dixon, Turetsky, Bilker, & Gur, 2002; Coffey et al., 1998), with the frontal and temporal lobes showing the greatest cortical atrophy (DeCarli et al., 2005). With regard to sex-related differences, males show more atrophy than females in the dorsolateral PFC by middle age (DeCarli et al., 2005; Gur et al., 2002; Cowell, Turestsky, Gur, Grossman, Shtasel, & Gur, 1994). The neurocognitive processes that are subserved by the temporal lobes and dorsolateral PFC (e.g., episodic memory and working memory) decline with age (e.g., Brittain, La Marche, Reeder, Roth, & Boll, 1991; Paolo, Troster, & Ryan, 1997; Salat et al., 2002); the decline in dorsolateral PFC functions might become more pronounced in females when estrogen is unavailable (e.g., when using estrogen suppressing medication). Regardless, the higher level of estrogen in females compared to males has been hypothesized to contribute to the neuroprotective effect on the dorsolateral PFC into middle age given the high numbers of estrogen receptors in this region (Eberling, Wu, Haan, Mungas, Buonocore, & Jagust, 2003; Cowell et al., 1994).

Estrogen and the Central Nervous System

Estrogen is a sex-steroid hormone that exerts effects on the body and central nervous system; it is primarily associated with female reproduction but also affects other processes, such as cognition. There are two main types of estrogen that occur in sexually mature non-pregnant females, estradiol and estrone, which vary in relative prominence throughout the lifespan. Estrogen begins to exert its influence on the human central nervous system prenatally, as androgens are converted to estradiol via aromatase, creating sex-related differences in structure and function, such as differences in the hypothalamus described earlier (McCarthy & Arnold, 2008). During puberty, the production of estradiol leads to further organizational effects in

females, such as the development of secondary sex characteristics, and begins to influence central nervous system functioning in a cyclical and transitory manner (Genazzani, Pluchino, Luisi, & Luisi, 2007).

In premenopausal adult females, estradiol, synthesized by the ovaries, is the primary estrogen circulating throughout the body, including the central nervous system (Rannevick, Jeppsson, Johnell, Bjerre, Laurrel-Borulf, & Svanberg, 2008). Estradiol circulates according to the menstrual cycle, from very low concentrations (close to 0 pg/mL) around the time of menstruation to higher concentrations (600 pg/mL) in the follicular phase prior to ovulation (Rosenberg, Pasternack, Shore, Koenig, & Toniolo, 1994). As females enter menopause, estradiol production declines to approximately 4 pg/mL (Cauley, Guiti, Kuller, LeDonne, & Powell, 1989), and the main source of estrogen in the body becomes estrone, a weaker form of estrogen, which is produced by adrenal glands, liver and kidneys through the conversion of androgens by aromatase. In males, levels of estradiol and estrone are typically under 50 and 60 pg/mL, respectively. Serum concentrations of estrone decrease slightly in women during menopause and through aging but not to the degree of estradiol (Cauley et al., 1989; Rannevick et al., 2008). Women who are postmenopausal often report side effects, such as hot flashes, weight gain, mood changes, and most germane to the present research, cognitive changes (Nelson, 2008).

Estrogens exert many functions through binding to estrogen receptors. Peripherally, estrogens bind to receptors in the uterus, bone, liver, heart, and breast, performing many functions including trophic functions, which can become pathological in certain instances. For example, approximately 70% of breast cancer cases are accelerated by estrogenic factors (Foulkes et al., 2004). Estrogen receptors alpha and beta are also found in the central nervous system, including areas that underlie cognition (Yaffe, Maki, & Schmidt, 2006). Estrogen

receptors have been found in the cerebellum, brainstem structures (e.g., locus coeruleus, raphe nuclei), the limbic system (e.g., amygdala and hippocampus), and cerebral cortex (Sherwin, 1997). Estradiol binds well to both receptors but estrone preferentially binds to estrogen receptor alpha (Gruber, Tschugguel, Schneeberger, & Huber, 2002). Although not well understood, both receptor types are distributed widely throughout the central nervous system and typically overlap; however, the distribution patterns and expression may be different and sex specific (Gonzalez et al., 2007; Shugrue, Lane, & Merchenthaler, 1997). For example, postmortem rodent and human studies show that ER beta is more prevalent in the hippocampus than ER alpha (Gonzalez et al., 2007; Shugrue et al., 1997), which may have implications for cognition.

Estrogen levels in adult females can be manipulated exogenously, either through the supplementation or suppression of the effects of estrogen. Estrogen supplementation is typically offered to perimenopausal females who are experiencing symptoms of menopause. The formulations used to supplement estrogen vary widely; for example, they can be natural or synthetic, derived from animals or plants, and include a single type of estrogen, such as estradiol, to a high number of estrogens, such as Premarin (Hogervorst, 2006). Hormone replacement therapy (HRT) was once thought to be protective to the body and brain, with reports of cognitive facilitation (e.g., Matthews, Cauley, Yaffe, & Zmuda, 1999; Schmidt et al., 1996; Zec & Trivedi, 2002). HRT use has declined significantly over the past five years due to the Women's Health Initiative finding that it caused an increased risk of dementia (Shumaker et al., 2003), heart attack and breast cancer (Writing Group for the Women's Health Initiative, 2002). Since the adverse effects of HRT were observed mainly in women over age 65 years, it is possible that the timing of the administration of estrogen (i.e., during perimenopause as opposed to many years post-menopause) or perhaps the type of HRT is responsible for the controversial findings regarding estrogen supplementation (Sherwin, 2004).

Estrogen can also be manipulated through suppression. Given the pathologically trophic effects of estrogen (e.g., the development of breast cancer), controlling growth by suppressing estrogen is important. Females with estrogenic breast cancer are typically offered estrogen suppressing medication as part of treatment, including tamoxifen and anastrozole, which are successful in preventing recurrence (ATAC Group, 2005). Tamoxifen and anastrozole work in different ways to suppress the effects of estrogen at the receptor site. Tamoxifen is a selective estrogen receptor modulator (SERM) that competitively binds with estrogen receptor alpha on the surface to reduce tumor growth (Bender, Paraska, Sereika, Ryan, & Berga, 2001). Although thought to be an antagonist in the brain, there is some suggestion that tamoxifen may have agonist or antagonist actions depending on the area of the brain (e.g., Zhou et al., 2002). Anastrozole is an aromatase inhibitor (AI) that prevents aromatase from converting androgens to estrogens to such an extent that it reduces serum estrone by up to 81% and serum estradiol by up to 84.9 % (Geisler, Haynes, Anker, Dowsett, & Lonning, 2002). Importantly, both tamoxifen and anastrozole exert effects beyond breast tissue, and appear to influence the central nervous system and neurocognition (e.g., Bender et al., 2007; Jenkins, Shillings, Fallowfield, Howell, & Hutton, 2004; Sumner, Grant, Rosie, Hegele-Hartung, Fritzemeier, & Fink, 1999).

Estrogen supplementation and suppression influence neural structure and metabolism. Increased blood flow and metabolism in the temporal and parietal lobes has been associated with estrogen supplementation in middle aged women taking hormone replacement therapy (Eberling, Reed, Coleman, & Jagust, 2000; Rasgon et al., 2001). The neural correlates of estrogen suppression have also been studied. For example, Eberling, Wu, Tong-Turnbeaugh, and Jagust (2004) demonstrated that tamoxifen use was associated with smaller hippocampal volume and decreased glucose metabolism, suggesting reduced brain activity, in the dorsolateral and inferior regions of the frontal lobes, regions that are associated with episodic and working memory

processes. Less is known about the effect of anastrozole on neural functioning (Berga, 2008), but theoretically it may exert similar effects to tamoxifen because it limits the amount of estrogen available for binding to estrogen receptors. The effects of tamoxifen and anastrozole, including their influence on the brain and cognitive functioning, have not yet been studied thoroughly; however, it is possible that these estrogen suppressors will have the biggest influence on neural areas with high levels of estrogen receptors and the neurocognitive abilities subserved by those areas.

Sex and Neurocognition

Given the sex-related differences and the influence of estrogen in the morphology and physiology of the central nervous system, it is not surprising that neurocognition is also affected by sex and estrogen. Most commonly, reports of sex-related differences in neurocognition include a male advantage for spatial neurocognition and female advantage for verbal measures. Males perform better than females on spatial perception and mental rotation tasks (e.g., Voyer, Voyer, & Bryden, 1995), mathematical reasoning and problem solving measures (e.g., Casey, Nuttal, Pezaris, & Benbow, 1995) and tests that require gross motor skill, such as targeting tasks (Sykes-Tottenham, Saucier, Elias, & Gutwin, 2005). Male advantages have also been reported for semantic memory (e.g., Snow & Weinstock, 1990), confrontational naming (e.g., Randolph, Lansing, Ivnik, Cullum, & Hermann, 1999; Welch, Doineau, Johnson, & King, 1996), spatial span (Orsini, Simonetta, & Marmorato, 2004), and visual memory (e.g., Reite, Cullum, Stocker, Teale, & Kozora, 1993; Roselli & Ardila, 1991), although these latter effects tend to be less consistent (e.g., Freides & Avery, 1991).

Several female advantages in neurocognition also have been documented. Females typically outperform males on verbal tasks, such as letter fluency (Bolla, Gray, Resnick, Galante, & Kawas, 1999; Crossley, D'Arcy & Rawson, 1997; Weiss et al., 2006), reading comprehension

(Hedges & Nowells, 1995), and spelling and grammar (Stanley, Benbow, Brody, Dauber, & Lupkowski, 1992). Females typically show an advantage over males for speeded manual dexterity tasks, particularly for the dominant hand (Bryden & Roy, 2005; Schmidt, Oliveira, Rocha, & Abreu-Villaca, 2000), and tend to outperform males on measures of complex visuomotor attention (Hedges & Nowells, 1995; Kaufman, McLean, & Reynolds, 1988; Snow & Weinstock, 1990). Although the female advantages in certain types of neurocognition are well established (e.g., Loonstra, Tarlow, & Sellers, 2001; Voyer, Postma, Brake, & Imperato-McGinley, 2007), it should be noted that not all studies report the expected effects (e.g., Mazaux et al., 1996; Tombaugh, Kozak, & Rees, 1999).

Perhaps related to the verbal advantage, females also outperform males on measures of verbal episodic memory (i.e., the recall of information tied to personal events and time), including immediate and delayed list learning (e.g., Kramer, Delis, & Daniel, 1988; Ragland et al., 2000) and story recall (e.g., Mann, Sasanuma, Sakuma, & Masaki, 1990; Norman, Evans, Miller, & Heaton, 2000). Interestingly, the female advantage for episodic memory appears to be unique to verbal memory, as there is usually no difference, or a male advantage, on visual episodic memory measures such as the Rey-Osterrieth Complex Figure Test (Lewin, Wolgers, & Herlitz, 2002; Reite et al., 1993; Roselli & Ardila, 1991). These findings suggest that the verbal contribution to a measure is important to elicit a female advantage.

Females also outperform males on certain object-location memory measures (Duff & Hampson, 2001; McBurney, Gaulin, Devineni, & Adams, 1997; Sykes-Tottenham, Saucier, Elias, & Gutwin, 2003; Silverman & Eals, 1992; Voyer et al., 2007). Object-location memory is the neurocognitive function that allows individuals to remember the locations of and relationships among specific objects, and functions in everyday life to help us navigate our environment and remember where we left certain objects (e.g., books, keys, etc.) or locate other objects (e.g.,

kitchen utensils). For example, Silverman and Eals (1992) found that females performed better than males when asked to identify which objects had moved locations from one array to the next, and Sykes-Tottenham et al. (2003) found a female advantage on a "Concentration" object-location memory task regardless of whether the task was presented in 2D or visually distorted. Although there is some controversy over the validity of the female advantage in object-location memory, because some researchers have reported null effects or a male advantage (Choi & L'Hirondelle, 2005; Gallagher, Neave, Hamilton, & Gray, 2006), a meta-analysis of object-location memory studies determined that the female advantage is indeed robust (Voyer et al., 2007). The female advantage appears to depend on the nature of the stimuli, type of task, and dependent measure (Voyer et al., 2007). For example, verbalizable geometric stimuli, but not difficult-to-verbalize uncommon stimuli, produce a female advantage.

The verbal contribution to object-location memory is an important area of study. In an attempt to reduce the verbalizability of the stimuli and rule out the female advantage for verbal information as an explanation for the effect, Eals and Silverman (1994) used uncommon objects (e.g., tool parts) for their object location memory task, and found that the female advantage for the task remained. In contrast, Choi and L'Hirondelle (2005) found that although females were more accurate than males on the common objects condition for an incidental object-location memory task, males were more accurate than females on the abstract condition. Although the authors used distance as a dependent measure, which typically produces a male advantage, the difference between their conditions suggests that verbalizability was mediating the effect. Further studies delineating the verbal contribution to the female advantage are needed.

Duff and Hampson (2001) reported a large female advantage for accuracy and time to completion on an object-location memory measure that used verbalizable stimuli. The task required participants to successfully match pairs of covered stimuli (i.e., colours or geometric

shapes) by looking at only two items at a time, requiring participants to remember the relationships among objects. Interestingly, the authors did not conceptualize their measure as an object-location memory task but instead described it as a visuospatial working memory measure. The task does have a significant working memory component because participants are required to hold information about objects and their relationships "online" while completing the task.

In brief, working memory is the neurocognitive process that allows us to hold, store, manipulate and maintain information "online" for short periods of time while other cognitive actions are taking place, and is used to guide action (Baddeley & Logie, 1999). Baddeley and Hitch's (1974) original working memory model was comprised of the phonological loop, the visuospatial sketchpad, and the central executive (Baddeley & Logie, 1999). The phonological loop manages short-term internal representations of verbal information, the visuospatial sketchpad manages short-term internal representations of visual and spatial information, and the central executive coordinates the internal representations of information, and transforms, manipulates, and links information with long-term memory processes (Baddeley & Logie, 1999). Baddeley (2000) has recently suggested a new component of the model: the episodic buffer. The episodic buffer provides a limited temporary store of multimodal information and integrates it into a temporal episodic representation. Neuroimaging evidence supports Baddeley and Logie's (1999) model of working memory; typically, central executive processing is linked to activation of the dorsolateral PFC on fMRI (e.g., D'Esposito, Postle, Ballard, & Lease, 1999), which is sexually differentiated and has a high number of estrogen receptors.

Arguably, Duff and Hampson's (2001) measure fits the description of both an object-location measure, as it requires participants to remember the locations of and relationships among specific objects, and a working memory measure, as it requires participants to hold the representations and relationships of the objects in mind while new information is simultaneously

presented and integrated, updating the stored content (Duff & Hampson, 2001). The authors also suggest that the female advantage on their measure is due to a sex-related difference in the central executive working memory component, subserved by the dorsolateral PFC, because of the active manipulation required while completing the task. They ruled out a phonological contribution due to the lack of sex-related differences on the digit span task, which reflects phonological slave processing.

Although Duff and Hampson (2001) ruled out alternative explanations for the female advantage for their measure, including sex-related differences in verbal ability, it is possible that the verbal component of the task contributed to the finding of a female advantage. The stimuli used in the task were easily nameable (i.e., crosses, squares, etc.), and since shapes are easy to label, participants were able to use a verbal strategy for the task. Consequently, it is possible that the female advantage found by Duff and Hampson (2001) reflects a female advantage for the verbal component rather than for the visuospatial working memory nature of the task. The use of non-verbal stimuli could help determine the verbal contribution to the measure.

Consistent with Duff and Hampson's (2001) assertion that their measure is a working memory measure, Speck et al. (2000) found a female advantage for verbal working memory using the "n-back" paradigm. The authors presented participants with a sequence of letters one after another, and asked them to respond when a stimulus matched a letter that had appeared in the sequence one, two, or three stimuli back (i.e., the 'n-back' task). Females were more accurate than males at correctly identifying the letters that had appeared 'n-back'. Speck et al. (2000) also used fMRI to investigate sex effects, and found that overall, the task activated dorsolateral PFC, and that females showed more left-lateralized neural activation compared to males when completing the tasks. Although Goldstein et al. (2005) did not observe a sex effect using a measure similar to the letter n-back task, they did find a different pattern of neural activation in

females compared to males. Neural activation increased in the inferior, middle, and orbital PFC in females compared to males while doing the task. Note that these are areas that tend to be sexually differentiated and have a high number of estrogen receptors as described earlier. Unfortunately, the relatively small sample sizes limit the generalizability of the behavioral data. Nagel, Ohannissien, and Cummins (2007) did perform a larger behavioral study, but did not find any sex-related differences using a letter and spatial n-back paradigm. Differences in the experimental procedure, however, make it difficult to compare to Speck et al. (2000). In fact, the n-back task is often confounded by degree of difficulty, as spatial versions of the task are typically much easier than verbal versions (Postle, D'Esposito, & Corkin, 2005).

Given the female advantage for Duff and Hampson's (2001) verbalizable object-location working memory measure and Speck et al.'s (2000) verbal n-back task, investigation of these measures beyond the verbal component is warranted. Duff and Hampson's (2001) task can be modified to manipulate the verbalizablility of the stimuli (e.g., common objects, geometric shapes, and abstract novel shapes) and the n-back task is easily adapted to other domains (e.g., spatial and object). Although the n-back task is widely used in neuroimaging studies, the behavioural data (e.g., sex and age effects) is not as strong (Nagel et al., 2007). Therefore, more studies investigating the sex effect on the n-back task without the constraints of neuroimaging (e.g., small sample sizes, uneven number of male and female participants) are needed.

Estrogen Supplementation and Neurocognition

Interestingly, both Duff and Hampson's (2001) object-location working memory measure and Speck et al.'s (2000) verbal n-back working memory measure have been used in the study of estrogen supplementation. The hypothesis that estrogen will influence performance on these working memory measures is reasonable given the high number of estrogen receptors in the dorsolateral PFC, which contributes to working memory processes. Hampson and Duff (2000)

found an advantage for females taking HRT (estrogen or estrogen/progesterone) compared to controls on their object-location working memory task. Similarly, Keenan et al. (2001) found that females taking estrogen via HRT had better performance than controls on auditory verbal versions of the n-back task, with the 2-back condition demonstrating the largest effect. These findings suggest that manipulation of estrogen influences performance on working memory measures.

Estrogen supplementation has been shown to influence other neurocognitive tasks, although the findings tend to be more variable than the research on sex-related differences in neurocognition. A fairly robust advantage for women taking estrogen replacement therapy has been found for verbal episodic memory, particularly for the immediate recall of paragraph recall (Zec & Trivedi, 2002). An estrogen supplementation advantage has also been found for complex visuomotor attention (Matthews et al., 1999) and speeded manual dexterity (Schmidt et al., 1996). Many unexpected nonsignificant findings, however, have also been reported. In fact, a meta-analysis by Low and Anstey (2006) found that none of the neuropsychological domains consistently showed significant improvement in association with hormone replacement therapy. Some of these inconsistencies might result from methodological problems, such as potential group differences in education, differences in age and hormone status upon initiation, differences in the underlying reason for starting HRT, and/or differences in compounds (Sherwin, 2004; Zec & Trivedi, 2002).

Estrogen Suppression and Neurocognition

Given the enhanced performance of estrogen supplementation on certain neurocognitive measures, including working memory measures, it is reasonable to hypothesize that the suppression of estrogen might lead to reduced performance on the same measures. The effect of estrogen suppression, using either tamoxifen or anastrozole, is less studied than estrogen

supplementation, but the small number of studies suggests that estrogen suppression has a deleterious effect on neuropsychological performance, particularly for measures sensitive to sex and estrogen. Anthony, Williams and Dunn (2001) found a decline in performance on short-term memory tasks in humans. Jenkins et al. (2004) examined the effects of tamoxifen and anastrozole on women with breast cancer and found that those taking the medication performed more poorly than controls on measures of immediate verbal episodic memory (i.e., a paragraph recall task) and complex visuomotor attention (i.e., a digit symbol copying task); no differences were found for visual memory, or verbal and visual working memory span (the authors did not include fluency or motor measures). Other studies have investigated the effect of estrogen-suppression on cognition, but are limited by the inclusion of women undergoing other forms of chemotherapy (Bender et al., 2007; Castellon, Ganz, Bower, Peterson, Abraham, & Greendale, 2004). Studies of breast cancer treatments on neurocognition show that chemotherapy has a negative effect (e.g., Brezden, Phillips, Abdollel, Bunston, & Tannock, 2000; Tchen, Wu, Shi, & Xu, 2002; van Dam et al., 1998), whereas radiation does not appear to affect neurocognition (Bender, Paraska, Sereika, Ryan, & Berga, 2001; van Dam et al., 1998).

Some research suggests that anastrozole in healthy women does not affect cognition. In a recent and rigorously controlled study, Jenkins et al. (2008) randomly administered anastrozole to women without a history of breast cancer and measured cognition at baseline and at three subsequent time-points. No differences across the time-points were found on any of the cognitive measures used in the study, including verbal memory and letter fluency. However, several measures that have been shown to be sensitive to the female advantage and the effect of estrogen were not included in the study. For example, speeded motor dexterity and complex visuospatial attention measures were not included. Notably, the authors did not report estrogen levels in their sample. Importantly, Duff and Hampson's (2001) object-location working

memory measure and the n-back task also were not part of Jenkins et al. (2008) battery. Given that Grigorova, Sherwin, and Tulandi (2006) found that premenopausal women taking an estrogen suppressing medication (leuprolide acetate depot) to the extent that estrogen levels were comparable to postmenopausal ranges had poorer performance than controls on a verbal and abstract objects n-back task, it is important to investigate the effect of estrogen suppression on working memory.

Goals

The first two studies in this dissertation research were designed to investigate whether the female advantage for working memory (Duff & Hampson, 2001; Speck et al., 2000) occurs beyond the verbal domain in young adults. Other memory systems have shown a sex-related effect for verbal information only; for example, Choi and L'Hirondelle (2005) found that the female advantage disappeared after the verbal component was removed. Study 1 replicates Duff and Hampson's (2001) object-location working memory by including verbalizable geometric shapes as stimuli and extends their work by also including stimuli that vary in degree of verbalizability (e.g., common objects vs. novel shapes). A secondary aim of the study was to compare a computerized version of the task (for ease of administration and scoring) to the manual version. Study 2 was designed to investigate whether the female advantage for verbal working memory is specific to verbal information or generalizable across domain (e.g., spatial, object). A secondary goal of Study 2 was to create more equivalent measures with regard to difficulty. Study 3 investigated the effects of estrogen suppressing medications (i.e., tamoxifen and anastrozole) taken by women with breast cancer on neuropsychological measures hypothesized to be sensitive to sex and estrogen, including the object-location working memory measure and the n-back working memory task described in Studies 1 and 2.

The proposed research will augment the relatively new and small body of research that has investigated sex-related differences, estrogen, and working memory. It will provide experimental data that can be interpreted within theoretical models. It also has clinical relevance for the women who are receiving estrogen suppression therapy as part of breast cancer treatment. Currently, the effects of estrogen suppressors, prescribed for treatment of breast cancer, on neuropsychological health has not been delineated well; there is still uncertainty about whether these medications affect neurocognition, and if so, how. Knowledge in this area has the potential to provide women with additional information about the side effects of medications so they may be fully informed when choosing treatments.

Running Head: GENDER AND OBJECT LOCATION MEMORY

The Female Advantage in Object Location Memory is Robust to Verbalizability and Mode of Presentation of Test Stimuli

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Abstract

This study extends Duff and Hampson's (2001) finding of a sex-related difference in favor of females for an object location memory task. Twenty female and 20 male undergraduate students performed both manual and computer-generated versions of the task using stimuli that varied in degree of verbalizability. A 2 x 2 x 3 ANOVA with Sex as a between-subjects factor, and Presentation (manual or computer) and Stimuli (common objects, common shapes and novel shapes) as within-subjects repeated measures revealed a significant main effect for Sex. Females made fewer errors than males regardless of presentation and across the three levels of verbalizability (i.e., stimulus types); moreover, the effect size was considered "large" (Cohen, 1988). These findings are interpreted within the context of the current literature that demonstrates a female advantage for object location memory (e.g., Voyer, Postma, Brake & Imperato-McGinley, 2007).

The Female Advantage in Object Location Memory is Robust to Verbalizability and Mode of Presentation of Test Stimuli

Object location memory is the cognitive ability that allows individuals to remember the locations of and relationships among specific objects, and functions in everyday life to help us remember where we left certain objects (e.g., books, keys, etc.) and navigate our environment (e.g., determining the location of kitchen utensils). Object location memory tasks typically require participants to make decisions about an array of objects each with a specific location; for example, participants may be asked to determine whether objects have moved locations (e.g., Silverman & Eals, 1992), how far objects have moved from an original position (e.g., Postma, Jager, Kessels, Koppeschaar & van Honk, 2004), and the relative positions among objects as new objects are presented (e.g., Duff & Hampson, 2001).

In a classic example of an object location memory task, Silverman and Eals (1992) presented participants with an array of common objects, and asked them to determine which objects had changed locations in a subsequent array. Interestingly, the authors found that females were more accurate than males at determining which objects had moved. Duff and Hampson (2001) found a similar female advantage for a different kind of object location memory task, which they described as having a substantial working memory component. The authors asked participants to match pairs of sequentially uncovered geometric figures in an array keeping all but the current objects hidden. The update and storage of information about the objects as they are revealed is consistent with working memory (Baddeley & Logie, 1999), while the requirement of explicitly memorizing the relationships among objects in specific locations is consistent with object location memory. Duff and Hampson (2001) found that females were more accurate than males when locating matching geometric shapes within the array; this effect size was "large" using Cohen's (1988) criteria ($d = 0.79$). The present study replicated and modified Duff and

Hampson's (2001) task to provide further evidence for the conditions under which the female advantage occurs.

Duff and Hampson's (2001) findings of a female advantage for object location memory add to the growing literature on sex-related differences in cognition. For example, there is a robust male advantage for certain spatial tasks, such as mental rotations (Voyer, Voyer, & Bryden, 1995) and targeting tasks (Sykes-Tottenham, Saucier, Elias, & Gutwin, 2005). In contrast, females typically show an advantage over males for speeded manual dexterity tasks (Bryden & Roy, 2005), phonological verbal fluency tasks (Weiss et al., 2006), verbal memory tasks (Kramer, Delis & Daniel, 1988) and, as mentioned, object location memory tasks (Silverman & Eals, 1992; Duff & Hampson, 2001; Sykes-Tottenham, Saucier, Elias, & Gutwin, 2003).

Although not all studies support the female advantage for object location memory (e.g., Choi & L'Hirondelle, 2005; Gallagher, Neave, Hamilton, & Gray, 2006), a recent meta-analysis conducted by Voyer, Postma, Brake and Imperato-McGinley (2007) supported an overall advantage for females on object location memory tasks. More specifically, however, Voyer et al. (2007) found that certain components influenced the sex-related difference for object location memory, as variations in the type of stimulus, type of task, and dependent measure impacted the female advantage. For example, geometric figure stimuli, explicit tasks (i.e., participants were told to remember objects in certain locations, in contrast to incidental tasks), and measures of accuracy and speed were all associated with a robust female advantage, whereas uncommon objects produced no sex effect and measures of distance (i.e., difference between actual position and participants' response) produced a male advantage.

Researchers have manipulated the verbal component of the test stimuli to delineate the female advantage for object location memory from the known female advantage for processing

verbal stimuli (e.g., Weiss et al., 2006). In an attempt to reduce the verbalizability of the stimuli, Eals and Silverman (1994) used uncommon objects (e.g., tool parts) on their object location memory task, and found that the female advantage for the task remained. In contrast, Choi and L'Hirondelle (2005) designed an incidental object location memory task that required participants to study either concrete or abstract objects (e.g., items that resembled part of an object) within an array. Participants were asked to replace the objects once they had been removed; distance was used as the dependant measure. Interestingly, Choi and L'Hirondelle (2005) found that although females were more accurate than males on the common objects condition, males were more accurate than females on the abstract condition, suggesting that degree of verbalizability was mediating the effect.

The present study sought to determine the conditions under which the female advantage for object location memory occurs by modifying Duff and Hampson's (2001) object location memory task. In light of Voyer et al.'s (2007) findings that object type influences the female advantage and Choi and L'Hirondelle's (2005) finding that males have an advantage for object location memory when abstract shapes are used, we were interested in investigating whether the geometric figures used by Duff and Hampson (2001) is robust to other types of stimuli, such as common objects and novel shapes. Thus, the verbalizability of test stimuli were manipulated, adding to the literature on the components that underlie object location memory. Specifically, common geometric shapes and common objects were used for the easy-to-verbalize conditions, and novel "Attneave" shapes, which are difficult to name and distinguishable (Vanderplas & Garvin, 1959), were used for the difficult-to-verbalize condition.

In another modification to Duff and Hampson's (2001) task, an equivalent computer version of the object location memory task, which used a computer mouse to uncover the flaps, was employed to determine the robustness of the female advantage as the component of task

presentation varied. This modification will also facilitate standardization, administration and scoring for the task in future studies. In other studies that manipulated task presentation, Voyer et al. (2006) found that a computerized version of the pencil and paper mental rotations task produced the same male advantage for the task, however, Dellatolas, Vanluchene and Coutin's (1996) found that the effect for the manual line bisection task changed from a leftward bias to a rightward bias as a result of presenting the task on the computer. It should be noted that Dellatolas et al. (1996) effect may have been confounded by distance, which varied with type of presentation; consequently, distance from the task was controlled in the present study. The fact that females are typically faster than males on speeded manual tasks (Bryden & Roy, 2005) may produce an attenuation for completion time on the computer task used in the present study, however, it was unknown how this would affect the gender difference for accuracy other than to attenuate any female advantage in test performance that was due to manual speed.

In summary, this study extended the female advantage for object location memory using Duff and Hampson's (2001) task. Specifically, females were expected to be more accurate than males on the easy-to-verbalize conditions (i.e., common objects and common geometric shapes) but not on the difficult-to-label condition (i.e., novel "Attneave" shapes). It is unknown whether the female advantage will be attenuated for accuracy on the computer version of the task compared to the manual version. The goals of the present study were to clarify whether or not previously reported sex-related differences in object location memory are related to the known female advantage in processing verbal stimuli, and to determine the robustness of this sex effect across manual and computer-generated modes of presentation.

Methods

Participants

Participants were recruited from the University of Saskatchewan Psychology Participants' Pool. Ethics approval was granted by the University of Saskatchewan Behavioral Ethics Research Board and informed consent was obtained prior to proceeding. Forty participants (20 male and 20 female) were included in the analyses. The average age for participants was 18.4 years for male participants (ranging from 17-27 years) and 20.2 years for female participants (ranging from 17-33 years).

Demographic information (e.g., age, handedness, etc.) was collected. Exclusionary criteria included uncorrected visual impairment, a history of significant neurological illness or injury, a history of severe psychiatric illness, nonfluent English, the use of medication that affects the central nervous system, and/or were over 35 years of age (to control for the effects of declining sex steroid hormones presumed to begin around age 35). Females taking hormonal birth control medication were kept in the study due to the large number of university students taking birth control.

Three participants were excluded due to a priori exclusionary criteria. In addition, 5 participants were lost due to experimental factors (1 was lost due to computer malfunction, 1 did not complete the task, and 3 were excluded from the analyses because they scored more than 2 standard deviations below the overall mean on 2 or more versions of the object location memory tasks, suggesting that they did not understand or could not complete the task).

Of the 40 participants included in the analyses, there were three left-handed participants (1 male and 2 female). Analyses of the data were completed with the left-handed sample included and excluded; the analyses were the same regardless, thus the left-handed sample was included in the final reporting of the data.

Materials

The experimental task (Duff & Hampson, 2001) was made of white foam board (20cm x 28cm; 38 cm diagonal), and had twenty foam board flaps (3.5 cm) to hide the stimuli (3cm). The visual stimuli were laminated and presented in black ink on white paper. The computer version of the experimental task (Gutwin, 2004) was created and run with JAVA script on a personal computer and was designed to be as close as possible to the manual version of the task. The experiment was run on a standard 15 inch computer monitor, and the background, flaps, and stimuli were the same colour and size as the manual version of the task. Participants sat with their forehead 40 cm from the manual and computer screens to control for distance from the task.

Experimental Tasks

Experimental Task (Duff & Hampson, 2001). The experimental task required participants to uncover flaps two at a time to find matching pairs of stimuli placed underneath the flaps. Twenty flaps (i.e., 10 matching pairs of stimuli underneath) were arranged in a 4 row x 5 column array. The stimuli for the three versions of this task included common geometric shapes, common objects, and novel shapes. The common geometric shape condition employed stimuli similar to those used by Duff and Hampson (2001) and included circles, stars, crosses, squares, trapezoids, and other namable geometric shapes. Different namable shapes were used in the manual and computer versions of the task in an attempt to avoid interference effects between the two presentation types.

The second set of stimuli was common objects similar to Snodgrass and Vanderwart (1992) images. The images were found at the International Picture Naming Project at the Centre for Reading and Language, University of California San Diego website (see Szekely et al., 2004). The objects were chosen so that there was an equal number from semantically different categories (e.g., fruit, vegetables, furniture, and transportation) and an equal number of typically

"male", female" and "neutral" images (McGivern et al., 1997). Again, there was no overlap in images between the manual and computer tasks. The pictures were presented in shaded gray scale because the quality was notably better than the black and white line drawings and are similar for naming agreement, familiarity, complexity, imagery judgments, and naming latencies (Rossion & Pourtois, 2004).

The novel shapes stimuli, which were relatively difficult to verbalize were "Attneave shapes" (Attneave & Arnoult, 1956), which are difficult to name and distinguishable (Vanderplas & Garvin, 1959). The Attneave shapes used in the present study were generated following Attneave's directions and then drawn on computer using the CorelDRAW drawing program version 8 (Corel Corporation, 1998).

Instructions for the task were the same as Duff and Hampson's (2001). Participants were shown the stimuli before beginning the task. Participants were asked to open two flaps at a time until they found all 10 matching stimuli, doing so in as few steps as possible. On the computer version, the two open flaps would close automatically if a third flap was clicked with the mouse. In keeping with Duff and Hampson (2001), as stimuli were matched, a copy of the matched stimuli was placed beside either the board or the computer so that participants knew they no longer needed to search for that particular pair, while the original matched pair remained under the flaps. Each participant performed one trial on all three versions of the task (i.e., common shapes, common objects, and novel shapes) both manually and on the computer. The order of presentation was counterbalanced and the locations of the stimuli within the array were randomized on each trial.

Dependent measures for the manual and computer versions included number of errors and time to completion. An error was made when a participant chose a pair of locations that had

already been searched but did not match, or when they re-searched an already matched pair. Time to completion was measured in seconds.

On a subset of participants (12 males and 13 females), a manipulation check was performed to determine whether participants were labeling the various stimuli. Participants were asked to name the various common objects, common shapes, and novel shapes.

Supplementary Tasks

Wide Range Achievement Test-3 (WRAT-3) Reading Subscale (Wilkinson, 1993). The WRAT-3 Reading subscale gives an estimate of verbal ability and is a moderate predictor of intelligence (Lucas, Carstairs, & Shores, 2003). According to the standardized instructions, participants were asked to read 42 words aloud and were given 10 seconds to read each word. The test was discontinued when participants either pronounced 10 words incorrectly or finished the test. Participants were given one mark for each word that was pronounced correctly, plus 15 points for correct baseline screening. The maximum score is 57.

Mental Rotations Test. (Vandenberg & Kuse, 1978). This task was administered to establish that male and female groups were representative of typical sex differences and would yield an advantage for males on this task. Participants were shown drawings of a target 3-D cubed object and were asked to determine which 2 of the 4 responses were the same objects rotated in space. Participants had 3 minutes to complete twelve questions and were given 1 mark for each correct answer and deducted .33 marks for incorrect answers. The maximum score for this task is 24.

Verbal Fluency Task. (FAS; Benton & Hamsher, 1989; Spreen & Strauss, 1998). An abbreviated version of the letter generation task was used to investigate verbal fluency and assess sex-related differences on the task. Participants were asked to name as many words as possible beginning with the letter “F”, excluding proper names (e.g., Frank) and variants of the same word

(e.g., "frank" and "frankly"). Participants were given 60 seconds to complete the task. One mark was given for each novel word.

Symbol Digit Modalities Test. (Smith, 1982). This task was administered to provide a control task for visual processing speed given the perceptual nature of the stimuli. During practice, participants were shown a key with symbols on the top and a corresponding number beneath each symbol. On the test, participants were given the symbols but were required to write in the corresponding numbers. Participants were given 90 seconds to fill in as many numbers as possible. One point was awarded for each correct response.

Procedure and design

After consenting, participants were tested individually in a private room using standardized instructions. In keeping with Duff and Hampson (2001), they were informed that although they would be timed, accuracy was most important. Participants completed one trial of all six conditions (i.e., common objects, common shapes, and novel shapes on both manual and computer versions of the task). The order of presentation was counterbalanced. Participants performed the experimental tasks before completing the supplementary tasks. Once participants had completed all measures, they were debriefed and given an opportunity to ask questions.

All analyses were performed using the Statistical Program for Social Sciences (SPSS) version 14.0. Analyses for the experimental task was a mixed 2 x 3 x 2 analysis of variance (ANOVA) with Sex (male and female) as a between-subjects factor, and type of Stimuli (common objects, common shapes, and novel shapes) and Presentation (manual or computer) as within-subject repeated factors. All within-subject comparisons are reported using Greenhouse-Giesser statistics. Repeated measures post hoc analyses were assessed using paired t-tests. The supplementary tasks were analyzed using independent t-tests with Sex (males and females) as the independent factor and score on the supplementary test as the dependent variable.

Results

Supplementary Tasks

Independent samples two-tailed t-tests were employed to examine differences between male and female performance on the supplementary tasks. Table 1 contains the means, standard deviations, and test statistics for each supplementary task. A conservative significance value ($p < .01$) was applied to reduce the likelihood of a Type I error. As shown in Table 1, no significant group differences were detected on the WRAT-3 estimate of intelligence, t (38) = 0.46, p =.65, the verbal fluency task, t (37) = 0.33, p =.75, or the Symbol Digit Modality Test, although the latter approached significance in favour of males, t (37) = 1.94, p =.06. Only the mental rotations task (MROT) reached significance, t (37) = 2.83, $p < .01$; as predicted, males produced more correct answers than females.

INSERT TABLE 1 ABOUT HERE

Experimental Tasks

The manipulation check revealed that although both male and female participants were able to label the common objects and common shapes readily, most males and females were unable to label the Attneave shapes readily. Specifically, 9 males and 7 females did not label any of the Attneave shapes specifically (e.g., “don’t know”, “no”, and “shape”), and 1 male and 4 females labeled only one of the Attneave shapes (e.g., “mountain”, “Z”, and “bowtie”). Only 2 males and 2 females labeled 2 or more of the Attneave stimuli, and no one labeled more than 4 of the shapes (note that 7 Attneave shapes were used in the manipulation check).

Experimental Task Errors. Table 2 contains the means and standard deviations for the number of errors for males and females during computer and manual presentations of common objects, common shapes, and novel shapes conditions. Mauchly’s Test of Sphericity, used to perform repeated-measures analyses, was violated for the Stimuli condition; therefore, more

conservative probability criteria were used (.01) for repeated measures analyses.

INSERT TABLE 2 ABOUT HERE

The 2 x 3 x 2 ANOVA produced no significant two-way or three-way interactions among Sex, Presentation, and Stimuli. The main effect for the between-subjects factor of Sex was significant, F (1, 38) = 6.93, p= .01, with females making fewer errors overall when compared to males. Females (M = 21.58, SE = 2.08) consistently made fewer errors across all conditions as compared to males (M = 29.33, SE = 2.08). Table 2 contains means and standard deviations for males and females across all conditions. An effect size (Cohen's d) was calculated for Sex and a "large" effect size (d = 0.82) was found (Cohen, 1988) across all conditions.

The analysis for number of errors also resulted in main effects for Stimuli, F (2, 76) = 55.19, p< .01, and for Presentation, F (1, 38) = 25.62, p< .01. Paired t-test post hoc analyses revealed that the three stimuli differed significantly from one another, with participants making the most errors on the novel shapes condition (M = 37.29, SE = 2.64), followed by the common shapes condition (M = 24.03, SE = 1.50), and finally the objects condition (M = 15.05, SE = 1.34). Participants (i.e., both males and females) also made fewer errors across all stimuli on the computer version (M = 20.68, SE = 1.60) as compared to the manual version (M = 30.23, SE = 1.92).

Time to Completion. Table 3 contains the means and standard deviations associated with time to completion in seconds for Sex, Presentation, and Stimuli. A 2 x 3 x 2 ANOVA for time to completion data revealed no significant three-way interactions. A significant interaction between Sex and Presentation, F (1, 38) = 6.46, p = .02. Females (M = 182.62, SE = 13.42) were faster than males (M = 204.40, SE = 13.42) on the manual task, whereas males (M = 177.05, SE = 9.47) were faster than females (M = 185.03, SE = 9.47) on the computer task. There were no other significant two-way interactions.

Significant main effects were observed for Stimuli, F (2, 76) = 68.35, p <.01, and Presentation, F (1, 38) = 83.65, p < .01, for time to completion. Paired t-test post hoc analyses indicated that all three Stimuli conditions differed from one another. Participants were fastest when completing the object condition (M = 111.53, SE = 6.42), followed by common shapes (M =203.06, SE =11.18) and novel shapes (M = 247.24, SE = 8.84). Finally, participants were faster overall on the computer (M = 181.04, SE =6.69) versus the manual presentation of all stimuli (M = 193.51, SE=9.49).

INSERT TABLE 3 ABOUT HERE

Discussion

This study provides additional support for a female advantage for object location memory and the components which influence the effect by extending Duff and Hampson's (2001) task. Specifically, degree of verbalizability of the stimuli (common objects, common geometric shapes and novel Attneave shapes) and mode of presentation (manual and computer) were manipulated to investigate possible limitations to the conditions under which females outperform males. It was hypothesized that females would outperform males on the common objects and common shapes conditions only, and it was uncertain whether the female advantage for accuracy would be attenuated on the computer task.

The present study found that females outperformed males overall by making fewer errors regardless of degree of verbalizability of the stimuli or presentation of the task. Notably, the effect size (d = 0.82) was "large" (Cohen, 1988) and consistent not only with Duff and Hampson (2001), but also with McBurney, Gaulin, Devineni and Adams (1997), who used a similar task that required participants to find matching cards within an array.

The finding that the female advantage occurred regardless of the degree of verbalizability of the stimuli is contrary to Choi and L'Hirondelle (2005), who found that the female advantage

disappeared when abstract difficult-to-label abstract stimuli were used in place of common objects. The reasons for the difference are unknown, but may be attributable to the differences in the task itself, type of stimuli employed, and dependent measure used. Firstly, in contrast to the present task, Choi and L'Hirondelle's task was an incidental task (i.e., participants were not explicitly told to remember certain objects in certain locations), which tends to be less reliable for a female advantage than explicit tasks (Voyer et al., 2007). Secondly, Choi and L'Hirondelle employed objects that may have been able to be coded by orientation, perhaps giving males an advantage because they were able to use a spatial strategy to code the objects. The novel Attneave shapes used in the present study were unlikely to be coded by orientation. Further research may compare the different types of abstract stimuli using the same task to determine how they affect performance. Finally, Choi and L'Hirondelle (2005) used distance as a dependent measure, which tends to produce a male advantage as compared to measuring accuracy or time to completion on object location memory tasks (Voyer et al., 2007).

With regard to the presentation of the task, participants overall made significantly fewer errors on the computer version of the task compared to the manual version of the task. Thus, although the computer version of the task appeared to measure the same construct and was easier to administer and score than the manual version, it is an easier task for both sexes. It is uncertain why accuracy was affected to this large degree, but one possible explanation is that holding the flaps open in the manual version was more taxing and visually more difficult for participants.

The present study has several limitations, one of which remains a challenge for researchers. Although the novel shapes were designed to reduce the verbalizability of the task, a manipulation check revealed that some of the participants (both males and females) used verbal labels for some of the novel Attneave shapes, either using familiar objects (e.g., "whale", "bow-tie") or letters of the alphabet. However, a large majority of participants did not label the novel

Attneave shapes, suggesting this condition was less of a verbal task than the common objects or common shapes. Although producing a purely nonverbal set of stimuli is difficult, if not impossible, the consistent female advantage across stimuli suggests that the female advantage is attributable to object location memory rather than verbal ability. This is further supported by the finding in this study of gender equivalency on the standardized neuropsychological measure of verbal fluency. Finally, all participants presumably used a verbal strategy for the object stimuli (e.g.., apple, dog, finger) as suggested by the manipulation check, yet this condition produced the same female advantage as the common shapes and novel shapes conditions. Future studies might systematically examine whether labeling novel shapes has an influence on performance.

Although a female advantage for object location memory was observed in the present study, we cannot say with certainty why it occurred. There is some suggestion that sex steroid hormones play a role in the advantage, as higher levels of estrogen in post-menopausal women have been associated with better performance on the task (Hampson & Duff, 2000), however, the present study did not measure estrogen levels. To complicate matters further, most female participants were taking long term hormonal birth control (i.e., depo-provera) making it difficult to discern stage of menstrual cycle and concomitant hormone levels. This might underlie the relative gender equivalency in the present study on the standardized neuropsychological measures that typically show a female advantage (i.e., verbal fluency, speeded visuomotor tasks). Despite gender equivalency on these measures, the female advantage on the object location working memory task was large and robust to type of stimuli and mode of presentation, at least as measured by error rates. It would be interesting to know how naturally circulating estrogen levels or manipulation of hormone levels through medications affect object location working memory performance; however, other factors, such as structural neuroanatomical differences and differences in neurotransmitter systems may contribute to these sex-related effects (Cahill, 2006).

Identifying a single underlying cause for the observed female advantage for object location working memory is likely a simplistic view of a complex phenomenon. It is probable that many interdependent early and current neurobiological factors as well as environmental factors work together to produce the effect. The results from this study underscore the importance of considering sex not just in experimental and clinical neuropsychological research and practice, but also when considering underlying neurobiology and real world applications.

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Table 1

Means, Standard Deviations, and Test Statistics for Supplementary Tasks

Supplementary Task	Mean	Standard Deviation	df	t-value
WRAT-3				
Males	48.95	3.02	39	0.46
Females	48.50	3.22	39	0.46
SDMT				
Males	67.58	11.22	38	1.94
Females	61.20	9.22	38	1.94
Letter Naming				
Males	14.45	3.82	38	0.33
Females	14.09	3.24	38	0.33
MROT*				
Males	11.25	3.60	38	2.83
Females	7.63	4.29	38	2.83

* indicates statistically significant finding at $p \leq .01$

Table 2

Experimental Task Number Errors across Mode of Presentation and Type of Stimuli

	Common Objects	Common Shapes	Novel Shapes
	Mean (SD)	*Mean (SD)*	*Mean (SD)*
Manual			
Males	22.45 (15.83)	36.75 (15.13)	47.95 (22.07)
Females	14.20 (9.32)	25.35 (14.05)	34.70 (21.42)
Computer			
Males	13.90 (7.27)	18.85 (15.70)	36.05 (20.40)
Females	9.65 (7.11)	15.15 (9.22)	30.45 (17.28)

Note. Females made significantly fewer working memory errors overall compared to males ($p \leq .01$).

Table 3

Experimental Task Time to Completion across Mode of Presentation and Type of Stimuli

	Common Objects	Common Shapes	Novel Shapes
	Mean (SD)	*Mean (SD)*	*Mean(SD)*
Manual			
Males	197.70 (122.37)	218.30 (65.63)	294.90 (88.73)
Females	154.10 (51.28)	206.70 (70.66)	269.05 (70.24)
Computer			
Males	102.75 (52.16)	120.60 (59.80)	210.10 (69.31)
Females	98.05 (37.55)	124.70 (43.37)	250.35 (101.16)

Note. Females were marginally significantly faster than males (time reported in seconds) on the manual version of the task, whereas males were faster than females on the computer version ($p = .02$).

Rationale for Study 2

Study 1 replicated and extended Duff and Hampson's (2001) findings of a female advantage on a task requiring working memory and object-location memory. The study extended the findings by manipulating the verbalilzability of the stimuli (i.e., common objects, geometric shapes, and novel shapes) on the object-location working memory measure. A computerized version of the measure was also created for ease of administration and scoring. The hypotheses for Study 1 were supported: females made fewer working memory errors than males on the object-location working memory measure regardless of the degree of verbalizability of the stimuli or mode of presentation (manual vs computer).

Given the female advantage found in Study 1, and the literature demonstrating a female advantage and estrogen advantage for working memory as assessed using the n-back task, particularly for verbal stimuli (Grigorova et al., 2006; Keenan et al., 2001; Speck et al., 2000), further investigation of the female advantage is warranted. The n-back task is easily adapted to various domains (e.g., verbal, spatial and object) but has typically been studied using the constraints of neuroimaging (e.g., small sample sizes, uneven number of male and female participants). For example, Speck et al. (2000) had a sample size of 17, and only investigated the sex-related difference using verbal stimuli. Therefore, Study 2 investigated whether the female advantage for verbal working memory using the n-back task is specific to verbal information or generalizable across domain (e.g., spatial, object). A secondary goal of Study 2 was to create more equivalent measures with regard to difficulty. It was expected that females would outperform males on a verbal and object version of the n-back task; however, males might be expected to perform better on the spatial version of the task given the spatial demands of the measure.

Running Head: SEX AND WORKING MEMORY

A Male Advantage for Spatial and Object but not Verbal Working Memory Using the N-Back Task

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Abstract

Sex-related differences have been reported for performance and neural substrates on some working memory measures that carry a high cognitive load, including the popular n-back neuroimaging paradigm. Despite some evidence of a sex effect on the task, the influence of sex on performance is seldom acknowledged but represents a potential confound in neuroimaging research. The present study investigated sex-related differences in verbal, spatial, and common object versions of the high cognitive load "n-back" working memory task. Eighteen male and 18 female undergraduates completed all 3 versions of the task. A mixed ANOVA, with Sex (male and female) as the between-subjects factor and Condition (verbal, spatial, and object) as the within-subjects repeated measure revealed that males were significantly more accurate than females on the spatial and object versions of the n-back task and performed equivalently to females on the verbal version of the task. Although the expected female advantage for verbal working memory was not found using this effortful n-back task, these results support a male advantage for high cognitive load spatial and object working memory. Future research should take into account the influence of sex on performance of the n-back task, and examine sex-related differences in working memory using other paradigms.

Introduction

The present study investigated sex-related differences in high cognitive load working memory measures using verbal, spatial, and object versions of the "n-back" task. The n-back task (e.g., Cohen et al., 1997; Gevins & Cutillo, 1993) is a continuous performance working memory measure that, in its higher cognitive load conditions (i.e., 2-back and 3-back), makes strong demands on working memory. The task is a popular paradigm for studying working memory in neuroimaging research, and has shown a female advantage for its verbal version (Speck, Ernst, Braun, Koch, Miller, & Chang, 2000) and is associated with sex-specific neural patterns (Speck et al., 2000; Goldstein et al., 2005). Despite this evidence, research on sex-related differences on the n-back task is lacking, and sex as a variable is seldom acknowledged in neuroimaging research. The different versions of the n-back task (e.g., verbal and spatial) also tend to vary in difficulty (e.g., Nagel, Ohannissien, & Cummins, 2007; Nystrom et al., 2000; Postle, D'Esposito, & Corkin, 2005), leading to another potential confound. Examining the influence of sex across different versions of the n-back task will add to the validity of the paradigm.

Sex-related differences in cognition are well established, with a male advantage found for spatial measures (e.g., Voyer, Voyer, & Bryden, 1995) and a female advantage found for many verbal measures (Crossley, D'Arcy, & Rawson, 1997; Kramer, Delis, & Daniel, 1988; Norman, Evans, Miller, & Heaton, 2000; Weiss et al., 2006) and object-location memory measures (Silverman & Eals, 1992; Sykes-Tottenham, Saucier, Elias, & Gutwin, 2003; Voyer, Postma, Brake, & Imperato-McGinley, 2007). A growing body of research supports sex-related differences for working memory measures that carry high cognitive loads. In addition to Speck et al.'s (2000) finding of a female advantage for the verbal n-back task and a number integer working memory task, Duff and Hampson (2001) and Lejbak, Vrbancic, and Crossley (2009)

reported a female advantage for an object-location task that had a significant working memory component. Studies of estrogen and the n-back task further support the notion of a sex-related difference on the paradigm. For example, Keenan, Ezzat, Ginsburg, and Moore (2001) found that estrogen supplementation facilitated performance on a verbal n-back task, and Grigorova, Sherwin, and Tulandi (2006) found that estrogen suppression worsened performance on both verbal and non-verbal n-back tasks.

Not all high load working memory studies have found a female advantage or a sex-related difference. A male advantage for a high cognitive load spatial working memory task (Cattaneo, Postma, & Vecchi, 2006) and a spatial span task has been reported (e.g., Orsini, Simonetta, & Marmorato, 2004), although not consistently (e.g., Robert & Savoie, 2006). Goldstein et al. (2005) found no effect for sex using a measure similar to the letter n-back task in a behavioral fMRI study, despite finding differences in neural activation (see above). Similarly, Nagel et al. (2007), who performed a strictly behavioral study, did not find any sex-related differences using a letter and spatial n-back paradigm. A degree of inhibition, however, was required in Nagel and colleagues task; participants were shown letters in different locations, and were instructed to respond to either the letters or the spatial position.

Although there is mainly overlap between the sexes for neural patterns associated with cognition, neural processing can vary with sex in degree of activation and neural region, particularly when the cognitive domain demonstrates a sex-related difference. For example, sex-related differences in neural activation have been found for spatial cognition (e.g., Hugdahl, Thomsen, & Ersland, 2006; Jordan, Wüstenberg, Heinze, Peters, & Jäncke, 2000), language (e.g., Baxtar et al., 2003; Weiss et al., 2003), and memory (e.g., Nyberg, Habib, & Herlitz, 2000; Piefke, Weiss, Markowitsch, & Fink, 2005). Sex-related differences in neural activation also have been reported for working memory tasks. For example, Speck et al. (2000) found less

lateralized activation in males compared to females on a verbal n-back task and integer working memory task. Using a measure similar to the n-back task, Goldstein et al. (2005) found a different pattern of neural activation in females compared to males (i.e., neural activation was higher for females in the middle, inferior, and orbital prefrontal cortex). In light of the contrasting findings regarding sex-related difference on n-back performance, and the different patterns of neural activation on this task, further investigation of sex-related differences on the n-back task is warranted.

The present study investigated sex-related differences in a high cognitive load n-back working memory task. Males and females were compared on verbal, spatial, and common object versions of the 2-back task. Based on previous research using high cognitive load working memory tasks, females were expected to outperform males on the verbal version (i.e., letter) of the 2-back task, and males were expected to perform at least equivalently or better than females on the spatial version (i.e., location) of the task. Although sex-related differences in object working memory have been investigated less extensively, we hypothesized that females would have an advantage for the object version (i.e., common objects) of the task, based on Duff and Hampson's findings (2001) and our report of a female advantage on common object-location memory (e.g., Lejbak et al., 2009), and McGivern, Huston, Byrd, King, Siegle and Reilly's (1997) report of a female advantage for object recognition memory. Also consistent with this hypothesis is the report by Postle et al. (2005) that object working memory is dependent on verbal substrates.

Establishing performance on the n-back task taking into consideration important normative individual differences, such as sex, will strengthen the n-back paradigm's utility to inform brain-behavior relationships. If a sex-related difference on the n-back task exists, it will encourage future research using the paradigm to consider the influence of sex. There may be

occasions when it is inappropriate to combine behavioral and neuroimaging data from both sexes. Finally, this research will advance the growing literature concerning sex-related differences and working memory, and potentially have theoretical implications for models of working memory.

Methods

Participants

Participants were recruited from a Department of Psychology undergraduate research pool. Ethics approval was granted by the university's Behavioral Ethics Research Board. Informed consent was obtained and demographic information (e.g., age, handedness, etc.) was collected in a brief paper-and-pencil questionnaire. A priori exclusionary criteria included nonfluent English, age greater than 35 years, uncorrected vision or hearing, and history of head injury, hormone disorder, or severe psychiatric disorder. Females taking hormonal birth control medication were included in the study due to the large number of university students taking birth control (i.e., over two-thirds in our sample).

One male was excluded because of nonfluent English, and 1 female was excluded due to age (i.e., over 35 years). Four left-handed participants (2 males and 2 females) were included in the analyses because they were evenly distributed between the groups and the pattern of results did not differ when they were excluded. One male and 6 females were excluded from the analyses because they performed below chance on one or more of the experimental tasks. After the exclusions, thirty-six participants (18 males; 18 females) were included in the final analyses. Average age was 18.6 (SD 1.2) years for males (age range = 17 to 21 yrs) and 19.1 (SD 2.8) years for females (age range = 17 to 28 yrs).

Materials

Supplementary Tasks

Estimate of verbal ability. The Wide Range Achievement Test, Third Edition (WRAT-3) Reading Subscale (Wilkinson, 1993) was used as an estimate of verbal ability (Spreen & Strauss, 1998, p 165). The task was administered and scored according to standardized protocol. The maximum raw score is 57.

Spatial ability. The Mental Rotations Test (Vandenberg & Kuse, 1978) was used to demonstrate sample representativeness on a cognitive task with established sex-related differences. Participants were shown line drawings of a target 3-D cubed object, and were asked to determine which 2 of the 4 responses were the same objects rotated in space. Participants had 3 minutes to complete 12 questions. One point was awarded for each correct answer, and .33 points were deducted for each incorrect answer. The maximum score is 24.

Experimental Tasks

N-back task. Verbal, spatial and common object versions of the n-back working memory task required participants to make decisions about the stimulus they saw "2-back" as each new stimulus was presented. The verbal n-back task consisted of a series of letters presented in the centre of the screen. The letters were lower case and presented in Courier New font with a font size of 72. All 20 consonants were used (vowels were excluded). To increase similarity to the verbal version, the spatial version consisted of a black circle (3 cm diameter) that moved around in 20 different locations (i.e., in a 4 row by 5 column array).

The common objects version of the n-back task included 20 objects that were similar to the images used by Snodgrass and Vanderwart (1992). The images were taken from the International Picture Naming Project at the Centre for Reading and Language, University of California San Diego website (see Szekely et al., 2004). The images have been shown to be similar to the Snodgrass and Vanderwart images for naming agreement, familiarity, complexity, imagery judgments, and naming latencies (Rossion & Pourtois, 2004). The objects were chosen

to ensure an equal number of semantic categories (e.g., fruit, vegetables, furniture, and transportation) and an equal number of typically "male", female" and "neutral" objects (McGivern et al., 1997).

Dependent measures for the n-back included number of correct answers and average reaction time. The maximum score for correct answers on each version is 168.

Procedure

After providing informed consent, participants filled out a brief demographic questionnaire and were tested individually in a private room using a standardized set of instructions. Participants performed the experimental tasks before completing the supplementary tasks. Each participant performed all three versions of the n-back task (the order of presentation was counterbalanced). Participants completed practice trials for each version of the n-back task, which gave immediate feedback on performance. For the practice trials and for the experiment, participants were asked to make comparisons between the current stimulus and the stimulus presented 2-stimuli prior (i.e., "2-back") by pressing a "yes" button if they were the same and a "no" button if they were different (the buttons alternated between "l" and "a").

Each version of the n-back task had a total of 168 trials (6 blocks of 28 trials), with a different number of "hits" within each trial, ranging from 8 to 13 (i.e., 36% hits). The order of the stimuli was randomly generated and pseudo-randomly ordered. In keeping with Speck et al. (2000), the stimuli were presented at the rate of 1 per second. Once participants completed the experimental and supplementary measures, they were debriefed and given an opportunity to ask questions.

Apparatus

The n-back tasks were created using the psychology experiment computer program E-Prime version 1.1. The experimental tasks were performed on a personal computer with a standard 15 inch computer monitor.

Analyses

All analyses were performed using the Statistical Program for Social Sciences (SPSS) version 14.0. The supplementary tasks were analyzed using Independent-Samples T-Tests with Sex (males and females) as the independent factor and score on the supplementary test as the dependent variable. Analyses for the experimental task was a mixed 2 x 3 analysis of variance (ANOVA) with Sex (male and female) as a between-subjects factor, and Version (verbal, spatial, and object) as the within-subject repeated measures. All within-subject comparisons are reported using Greenhouse-Giesser statistics. Between-group (i.e., Sex) post-hoc analyses were assessed using Independent-Samples T-Tests with Sex as the independent factor and the experimental test as the dependent variable. Repeated measures post hoc analyses were assessed using Paired-Samples T-Tests with the different versions of the n-back task forming the paired factors.

Results

Supplementary Tasks

The estimate of verbal ability (WRAT-3 Reading) did not differ statistically between the two groups, t (34) = 1.11, p =.28, with males ($\overline{x}$ = 49.3, SD = 2.3) performing similarly to females ($\overline{x}$ = 48.0, SD = 3.7). As expected, the measure of spatial ability (MROT) differed between the two groups, t (34) = 2.53, p= .03, with males ($\overline{x}$ = 11.1, SD = 3.8) producing significantly more correct answers than females ($\overline{x}$ = 8.0, SD = 5.0).

Experimental Tasks

Sphericity, assessed by Mauchly's Test of Sphericity, was not violated for the different

versions (i.e., verbal, spatial, and semantic) of the task. The 2 x 3 ANOVA produced a significant main effect for the between-subjects factor of Sex, F (1, 34) = 5.51, p= .03. Males were significantly more accurate than females across the three versions of the "2-back" working memory task, with a "medium" effect size (d = 0.78) as demonstrated by Cohen's d (Cohen, 1988). There was also a main effect for Version, F (2, 68) = 6.48, p< .01. Post-hoc Paired T-Tests revealed that all participants performed significantly worse on the verbal version compared to the spatial, t (35) = 2.73, p = .01, and object, t (35) = 2.73, p = .01, versions, which did not differ significantly from one another, t (35) = 0.23, p = .82.

The main effects, however, were tempered by a significant interaction between Sex and Version, F (2, 68) = 6.89, p < .01. Post-hoc independent t-test analyses revealed that males outperformed females on the spatial, t (34) = 3.26, p < .01, and object, t (34) = 2.74, p = .01, versions of the task, and that the two groups did not differ on the verbal version, t (34) = 0.19, p =.85. Table 1 contains the means and standard deviations for accuracy according to sex on the different versions of the n-back task.

As shown in Table 1, when the groups were examined separately, females performed similarly across the different versions of the tasks, whereas males performed significantly better on the spatial, t (17) = 5.86, p<.01, and object, t (17) = 3.92, p<.01, as compared to the verbal version of the task.

INSERT TABLE 1 ABOUT HERE

As others have reported in similar n-back research (e.g., Parmenter et al., 2006) some participants skipped responses during this speeded and highly effortful task. Consequently, the number of non-responses was analyzed to investigate possible differences in strategy use between males and females across versions of the 2-back task, which potentially could account for some of the sex-related differences described above. A repeated measures ANOVA with the same

independent variables entered in the initial analysis and the dependent variable of number of skipped responses was performed. No interactions were found. There was a trend toward a main effect for sex for non-responses, F (1, 34) = 3.74, p=.06, with females having significantly higher rates ($\bar{x}$ = 11.76., SE =1.83) compared to males ($\bar{x}$ = 6.77, SE = 1.83). When analyses were re-run with non-responses deleted, the main effects for Sex, F (1, 34) = 2.66, p=.12, and Version, F (2, 68) = 2.30, p=.11, were lost, but the interaction between Sex and Version remained significant, F (2, 68) = 8.72, p = <.01. Post-hoc independent t-test analyses revealed that males outperformed females on the spatial, t (34) = 2.44, p=.02) version, with a trend toward a male advantage on the object version, t (34) = 1.80, p =.08. As in the preliminary analyses, males and females did not differ on the verbal version of the "2-back" task, t (34) = 0.33, p =.75.

Reaction Time. A 2 x 3 ANOVA for average reaction time resulted in a significant main effect for Version, F (2, 68) = 18.18, p = <.01. Post hoc tests revealed that all conditions differed from one another significantly for reaction time (i.e., verbal-spatial, t [34] = 5.66, p<.01; verbal-object, t[34] = 4.06, p<.01; and spatial-object, t [34] = 2.46, p=.02). Participants were fastest on the spatial version, intermediate on the object version and slowest on the verbal version. The main effect for Sex did not reach significance, F (1, 34) = 0.14, p =.72, nor did the interaction between Sex and Version, F (2, 68) = 0.33, p =.72. Analyses were also performed for reaction time using correct responses only, but no sex effects or interactions were found.

Discussion

The present study investigated the effect of sex on a higher cognitive load version of the n-back working memory task across different task domains (i.e., verbal, spatial, and object). The n-back paradigm is a popular working memory paradigm in neuroimaging research, but the influence of sex is seldom acknowledged despite reports of a female advantage (Speck et al.,

2000) and different patterns of neural activation (Goldstein et al., 2005; Speck et al., 2000). The impact of individual differences, such as sex, on task performance is important because it might prove to be a potential confound in the interpretation of brain-behavior relationships in working memory.

Specifically, we compared male and females on verbal, spatial, and object working memory measures using the 2-back version of the n-back task. We expected that females would outperform males on the verbal and object versions, and males would outperform females on the spatial version of the n-back task. Only one of our hypotheses was supported. As expected, males performed significantly better than females on the spatial version of the n-back task. This finding is consistent with other researchers who have found a male advantage for spatial working memory for both spatial span (Orsini et al., 2004) and visuospatial working memory under high load conditions (Cattaneo et al., 2006), and can be placed within the larger context of a male advantage for many other measures of spatial ability (e.g., Voyer et al., 1995). Future studies may delineate the factors contributing to the male advantage (e.g., the relative contributions of spatial ability versus working memory) and whether the male advantage occurs across different spatial configurations (e.g., number of different positions, easy and hard targets).

Contrary to our hypothesis, males outperformed females on the common object version of the n-back task. We expected that females would perform better than males, given McGivern et al.'s (1997) finding of a female advantage for object recognition, the female advantage observed using similar stimuli with an object-location memory task (Lejbak et al., 2009) and the presumed verbal component of the common objects task (Postle et al., 2005). The unexpected male advantage for object working memory might be related to the observed male advantage in some forms of semantic memory; for example, some studies show a male advantage for a measure of confrontational naming (Welch, Doineau, Johnson, & King, 1996), which has line drawings

similar to the objects we used. The n-back task is a versatile paradigm that is used to study many different types of working memory, including letters (e.g., Awh, Jonides, Smith, Schumacher, Koeppe, & Katz, 1996; Jonides et al., 1997; Speck et al., 2000) words (e.g., Kim, Kim, Lee, Lee, Lee, & Kwon, 2002), locations (e.g., Smith, Jonides, & Koeppe, 1996; Nystrom et al., 2000), shapes (e.g., Hautzel et al., 2002; Nystrom et al., 2000), faces (e.g., Braver et al., 2001), and common objects (e.g., Hautzel et al., 2002). Future studies are needed to investigate the effect of sex using different objects to determine whether the male advantage is specific to common namable objects, or generalizable to shapes, faces, and other object working memory stimuli.

The hypothesis that females would outperform males on the verbal version of this measure was unsupported. These findings are inconsistent with Speck et al. (2000), who found that females outperformed males on a verbal version of the n-back task and on other similar verbal working memory measures. The results, however, are consistent with Goldstein et al. (2005) and Nagel et al. (2007), who did not find sex-related differences in performance on similar verbal working memory tasks. It should be noted that although Goldstein et al. (2005) did not find sex-related behavioral differences on similar working memory measures, both Speck et al. (2000) and Goldstein et al. (2005) found sex-related differences in brain activity during the task, with females showing more lateralization to the left (Speck et al., 2000) and higher activation in the middle, inferior and orbital prefrontal cortex (Goldstein et al., 2005) compared to males. These differences may reflect a different strategy in females compared to males.

Although not the primary purpose of this study, we found that females may have used a different strategy than males to complete the task. Females skipped items more often than males, presumably to make the task more manageable. After eliminating non-responses, however, the male advantage for spatial working memory remained, although the male advantage for object working memory was reduced to a trend. Parmenter et al. (2006) employed a scoring system that

takes skipped data into account (e.g., "dyads" and "chunking"), which may be useful in future studies; however, Parmenter et al. suggest that the scoring system is most useful when accuracy is equivalent but differences in strategy are suspected. In our case, the number of skipped stimuli might simply reflect females' relative difficulty with the task as opposed to a difference in strategy, since famales skipped responses at similar rates across the verbal, spatial, and object conditions.

The n-back measures in the present study were designed to be comparable in terms of difficulty across the different versions in light of reports by several researchers that domains differ on this important characteristic (Nagel et al., 2007; Nystrom et al., 2000; Postle et al., 2005). We demonstrated that the versions were equivalent in terms of difficulty for females; although the spatial and object versions were easier for males than the verbal version. Given these sex-related differences, it may be unreasonable to expect equivalent performance across all measures. It is interesting that for both males and females, performance on the spatial and object versions of the task was similar, despite presumed differences in degree of verbalizability. In contrast, males performed uniquely and relatively more poorly on the verbal version of the "2-back" task Future studies may investigate this difference systematically. For example, it is possible that females, but not males, use a verbal strategy across all versions of the task, which results in less optimal performance for males on the verbal version of the task. Theoretically, it is also possible that central executive functions are relatively amodal or a unitary construct in females compared to males.

The present research has important implications for behavioral and imaging studies of brain function. When n-back tasks tapping into the different types of working memory (e.g., verbal and spatial) were similar with regard to difficulty, sex-related differences emerged. We encourage other researchers using the n-back paradigm to consider using more challenging

versions of the spatial condition to reduce the confound of difficulty, and to consider sex-related differences as potential influences on performance. Finally, researchers can productively use measures outside the n-back paradigm to study sex-related differences and working memory in behavioural and neuroimaging research. The finding of sex-related differences also suggests a dissociation of verbal and spatial working memory for males, but not females, which may have important implications for our conceptualization of working memory. The fact that both Speck et al. (2000) and Goldstein et al. (2005) found different patterns of neural activation between the sexes suggests that sex-related differences exist on this task that are not always observed in performance. We did not directly examine neural substrates, but suggest that the use of different paradigms, methodologies, and statistical analyses in neuroimaging research will aid in establishing the similarities and differences in neural patterns of functioning for working memory. Despite these cautions, the n-back task has been a very useful tool in the study of working memory in a variety of populations, such as normal aging (Kwong & Ryan, 1995; Salat, Kaye, & Janowski, 2002), individuals with schizophrenia (e.g., Kim et al., 2003; Krieger, Lis, Cetin, Gallhofer, & Meyer-Lindenberg, 2005) and individuals with multiple sclerosis (e.g., Cader, Cifello, Abu-Omar, Palace & Matthews, 2006; Parmenter, Shucard, & Shucard, 2007).

The present study has several limitations. In keeping with Speck et al. (2000), the stimuli were presented at the rate of 1 per second, which is faster than most studies report. The rate of presentation of stimuli in the n-back task is not standardized and varies widely, with reports of 1s (Speck et al., 2000) and 1.5s (Hautzel et al., 2002), with most studies using a rate of approximately 2s to 3s (e.g., Nystrom et al., 2000; Parmenter et al., 2006; Salat et al., 2002). Furthermore, imaging constraints leave the pace at as high as 7s to 8s (Costa, Peppe, Dell'Agnello, Caltagirone & Carlesimo, 2009; Postle et al., 2005). Regardless, our rates of

accuracy are very similar to other published reports (e.g., McMillan, Laird, Witt, & Meyerand, 2007; Nagel et al., 2007), suggesting that rate of presentation is not a key concern.

Another limitation of this study is that we did not manipulate cognitive load, but used only a high-load "2-back" task. Future studies are needed to investigate whether the sex-related differences occur in the "1-back" and "3-back" conditions. We also had a high number of participants who scored below chance on at least one of the versions (i.e., one male and six females). The fact that more females than males were unable to complete the measure, and were thus excluded from the subsequent analyses, suggests that the male advantage may be even more pronounced than what we have reported here, and the below chance performances may simply represent females' relative difficulty with the task. In fact, performance patterns for the object and spatial versions of the task are similar to those seen in studies of the male advantage for certain spatial tasks (e.g., mental rotations), suggesting an underlying spatial contribution to the task. Similarly, the task may share elements similar to the paced auditory serial addition task (PASAT), which has also shown a male advantage (Brittain, Marche, Reeder, Roth & Boll, 1991). Although some of the participants not included in the analyses also had difficulty with the supplementary tasks and estimates of verbal intelligence, others did not. Future studies are needed to investigate the reasons why some participants had difficulty with the task (e.g., general ability, state anxiety) and to differentiate these from systematic sex-related differences (e.g., motivation, spatial experience).

Finally, given the sex-related differences found in the present study, it would be interesting to further delineate the effects of sex-steroid hormones on the n-back task. Keenan et al. (2001) found that postmenopausal women taking estrogen performed better than controls on an auditory digit version of the n-back task, and Grigorova et al. (2006) found that premenopausal women taking leuprolide acetate depot, an estrogen suppressing agent, performed

worse than controls on verbal and non-verbal n-backs. As a university sample, our female participants had a high rate of long-acting oral contraceptive rates, so we were not able to look at menstrual cycle or hormone effects systematically. A worthwhile area of study would be to determine how naturally circulating estrogen levels affect performance, and whether the supplementation or suppression of estrogen has an effect. We examined middle-aged and older adults undergoing treatment for estrogenic breast cancer with endocrine therapy and age-matched controls on the n-back task (Lejbak, Vrbancic & Crossley, in press), and found no differences between the groups. It should be noted that older women had difficulty completing the task. Further research is needed to determine whether the difficulty completing the task was related to sex or age, or another variable. Finally, the results from the present study underscore the importance of considering sex not just in experimental and clinical neuropsychological research and practice, but also when considering underlying neurobiology and real world applications.

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Table 1

Means, Standard Deviations, and Effect Sizes for Verbal, Spatial, and Object Working Memory Accuracy Scores

	Group		
	Females	Males	
N-Back Version [a]	Mean (SD)	Mean (SD)	Cohen's *d*
Verbal	131.39 (18.01)	132.78 (18.55)	0.08
Spatial	130.11 (20.93)	149.11 (13.13)	1.09*
Object	132.44 (21.46)	147.89 (10.53)	0.91*

[a] Scores are number correct, with a maximum score of 168.

* $p<.05$

Rationale for Study 3

Studies 1 and 2 investigated the female advantage for working memory using verbal and non-verbal stimuli. Study 1 demonstrated a female advantage for accuracy on a task (Duff & Hampson, 2001) requiring working memory and object-location memory regardless of the degree of verbalizability of the stimuli. In contrast, Study 2 did not find a female advantage for working memory using the n-back task, and in fact found a male advantage for the spatial and object versions; there was no sex-related difference for the verbal version. Both Duff and Hampson's measure and the n-back task have been used to demonstrate that estrogen supplementation in postmenopausal women via hormone replacement therapy facilitates performance on these measures (Hampson & Duff, 2000; Keenan et al., 2001). Furthermore, the suppression of estrogen in premenopausal women has been shown to have adverse effects on performing the n-back task (Grigorova et al., 2006). Therefore, although mixed results with regard to the female advantage were found in Studies 1 and 2, further investigation into the effects of estrogen on these measures is warranted. Additionally, the literature investigating the effects of endocrine therapy in breast cancer on other cognitive measures is equivocal (e.g., Jenkins et al., 2004; Jenkins et al., 2008) and would benefit from further study.

Study 3 investigated the effects of estrogen suppressing medications (i.e., tamoxifen and anastrozole) taken by women with breast cancer on the object-location working memory measure and the n-back working memory task described in Studies 1 and 2. Participants also completed a full neuropsychological battery of tests that included measures that are typically sensitive to estrogen (i.e., show a female advantage, performance facilitation with estrogen supplementation, or performance debilitation with estrogen suppression), such as verbal episodic memory, and measures that are typically insensitive to estrogen, such as attention. It was hypothesized that women undergoing endocrine therapy as part of breast cancer treatment would perform worse

than healthy controls on estrogen-sensitive measures, including the shapes and objects object-location working memory measure and verbal n-back task used in Studies 1 and 2.

Running Head: ENDOCRINE THERAPY AND COGNITION

Endocrine Therapy is Associated with Low Performance on Some Estrogen-Sensitive Cognitive Tasks in Postmenopausal Women with Breast Cancer

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Abstract

This study investigated the effects of endocrine therapy (i.e., tamoxifen and anastrozole) on cognitive functioning by comparing 28 postmenopausal women with breast cancer to 37 healthy age-equivalent controls. Participants completed neuropsychological tests previously shown to be estrogen-sensitive (e.g., verbal memory, letter fluency). A significant treatment effect was observed on speeded measures of letter fluency, complex visuomotor attention, and manual dexterity, but not on measures of verbal or object-location memory, or on tests presumed to be estrogen-insensitive (e.g., spatial ability). In partial support of previous research, these results indicate that endocrine therapy can have detrimental effects on speeded higher brain functions but not necessarily on memory.

Introduction

This study investigated the effect of endocrine therapy (i.e., tamoxifen and anastrozole), prescribed in the treatment of estrogen sensitive breast cancer, on neuropsychological domains presumed to be sensitive to the effects of estrogen (e.g., verbal episodic memory, object-location memory, letter fluency, complex visuomotor attention, speeded manual dexterity, and certain kinds of verbal working memory). Tamoxifen and anastrozole are widely used to treat estrogen sensitive breast cancer and are successful in preventing its recurrence (ATAC Group, 2005; EBCTCG, 2005). The medications work in different ways to suppress estrogen at the receptor site[1], but importantly, both exert effects beyond breast tissue, and appear to influence the central nervous system and neurocognition (e.g., Bender et al., 2007; Jenkins, Shillings, Fallowfield, Howell, & Hutton, 2004; Sumner et al., 1999). Given the success of these medications in preventing recurrence of breast cancer, and the length of time they are taken (typically five years), the investigation of their side effects, including neurocognitive side effects, is an important investigative area.

The supplementation and suppression of estrogen impacts neural blood flow and metabolism in women. The brain is rich in estrogen receptors, particularly in the prefrontal cortex and hippocampus (McEwan & Alves, 1999; Shughrue & Merchenthaler, 2000); increased blood flow and metabolism associated with estrogen supplementation have been observed in the temporal and parietal lobes (Eberling, Reed, Coleman, & Jagust, 2000; Rasgon et al., 2001). Estrogen suppression also appears to influence neural structure and metabolism. For example, Eberling, Wu, Tong-Turnbeaugh, and Jagust (2004) demonstrated that tamoxifen use was associated with smaller hippocampal volume and decreased glucose metabolism in the

[1] Tamoxifen is a selective estrogen receptor modulator (SERM) that blocks the binding of estrogen to estrogen receptors, whereas anastrozole is an aromatase inhibitor (AI) that reduces the amount of circulating estrogen by preventing the conversion of androgen to estrogen

dorsolateral and inferior regions of the frontal lobes. Less is known about the effect of anastrozole on neural functioning (Berga, 2008). Theoretically it should exert similar effects to tamoxifen because it limits the amount of estrogen available for binding to estrogen receptors; however, in contrast with aromatase inhibitors (e.g., anastrozole), selective estrogen receptor modulators (e.g., tamoxifen) also have agonistic effects on specific receptors (e.g., Mourits, De Vries, Willemse, Ten Hoor, Hollema & Van Der Zee, 2001; Zhou et al., 2002).

In addition to estrogen's influences on the structure, blood flow, and metabolism of the central nervous system, several lines of evidence document its influence on cognition. Studies of sex-related effects, which capitalize on the natural differences in estrogen levels between males and females, show that females typically outperform males on measures of immediate and delayed verbal episodic memory (Kramer, Delis, & Daniel, 1988; Norman, Evans, Miller, & Heaton, 2000), object-location memory (Duff & Hampson, 2001; Lejbak, Vrbancic, & Crossley, 2009; Silverman & Eals, 1992; Sykes-Tottenham, Saucier, Elias, & Gutwin, 2003; Voyer, Postma, Brake, & Imperato- McGinley, 2007), letter fluency (Crossley, D'Arcy, & Rawson, 1997; Loonstra, Tarlow, & Sellers, 2001; Weiss et al., 2006), complex visuomotor attention (Kaufman, McLean, & Reynolds, 1988; Snow & Weinstock, 1990), speeded manual dexterity, particularly for the dominant hand (Bryden & Roy, 2005; Schmidt, Oliveira, Rocha & Abreu-Villaca, 2000) and certain types of verbal working memory (Speck et al., 2000). Although the female advantages in cognition are well established (e.g., Loonstra et al., 2001; Voyer et al., 2007), it should be noted that not all studies report the expected effects (e.g., Mazaux et al., 1995; Tombaugh, Kozak, & Rees, 1999), and the female advantage for verbal working memory, in particular, appears to depend on the test used to measure this higher brain function. For example, simple measures of digit span do not typically show significant sex-related differences (e.g., Duff & Hampson, 2001).

Research on the effects of estrogen supplementation on cognition provides additional support for the influence of estrogen in the central nervous system, although the findings tend to be more variable than the research on sex-related differences in cognition. A fairly robust advantage for women taking estrogen replacement therapy has been found for verbal episodic memory, particularly for the immediate recall of verbal discourse (i.e., orally presented paragraphs) (Zec & Trivedi, 2002). An estrogen supplementation advantage has also been found for object-location memory (Hampson & Duff, 2000), complex visuomotor attention (Matthews et al., 1999), speeded manual dexterity (Schmidt et al., 1996), and certain verbal working memory tasks, such as a digit ordering task (Hampson & Duff, 2000) and an auditory n-back task (Keenan, Ezzat, Ginsburg, & Moore, 2001).

Firm conclusions about the effects of estrogen supplementation on cognition, however, must be tempered by the many nonsignificant findings. For example, Hampson and Duff (2000) did not find an advantage for verbal episodic memory and Keenan et al. (2001) did not find an advantage for letter fluency. In fact, a meta-analysis by Low and Anstey (2006) found that none of the neuropsychological domains consistently showed significant improvement in association with hormone replacement therapy. Some of these inconsistencies might result from methodological problems, such as potential group differences in education (Zec & Trivedi, 2002), differences in age when estrogen replacement therapy was initiated, or differences in duration of therapy. For example, Sherwin (2004) proposed a critical window for estrogen supplementation (i.e., administration to women under age 65 years) to influence cognition. Similarly, underlying differences in the reason for estrogen supplementation (e.g., peri- or post-menopausal symptoms vs surgically- or chemically-induced menopause) might result in study inconsistencies.

The effect of estrogen suppression on cognition is a relatively new, but important, area of research in light of the potential impact of endocrine therapy prescribed in the treatment of

estrogen sensitive breast cancer. Jenkins et al. (2004) examined the effects of tamoxifen and anastrozole on women with breast cancer and found that those taking the medications performed more poorly than age-matched controls on measures of immediate verbal episodic memory (i.e., a paragraph recall task) and complex visuomotor attention (i.e., a digit symbol copying task); no differences were found for visual memory, or verbal and visual working memory span (the authors did not include fluency or motor measures). Similarly, Collins, Mackenzie, Stewart, Bielajew, and Virma (2009) found that women taking tamoxifen and anastrozole for breast cancer performed more poorly than healthy controls on processing speed and verbal memory measures. In a recent and rigorously controlled study, Jenkins et al (2008) randomly administered anastrozole to women without a history of breast cancer and measured cognition at baseline and at three subsequent time-points. No differences across the time-points were found on any of the cognitive measures used in the study, including verbal memory and letter fluency; however, the results of the study were limited by high rates of women discontinuing the medication due to side effects (Berga, 2008) and potential practice effects, and did not include some estrogen-sensitive measures, such as speeded manual dexterity, and object-location memory.

Other studies have investigated the effect of endocrine therapy on cognition, and typically find some degree of cognitive impairment in women undergoing endocrine therapy, but are limited by the inclusion of women undergoing chemotherapy[2] (Bender et al., 2007; Castellon et al., 2004; Schagen, Muller, Boogerd, Mellenbergh & van Dam, 2006). Interestingly, a recent prospective study found no cognitive differences in women undergoing chemotherapy and

[2] Chemotherapy independent of endocrine therapy use is associated with cognitive changes in women with breast cancer (Tchen et al., 2003; Brezden, 2001), whereas radiation is not (van Dam et al., 1998; Bender et al. 2001).

endocrine therapy as part of breast cancer treatment, and actually found improvements on certain cognitive measures across time (Hermelink, Henschel, Untch, Bauerfeind, Lux, & Munzel, 2008). One limitation is that the women were undergoing other forms of therapy (i.e., chemotherapy) during the study, and it might be expected that cognition improved after completing chemotherapy. Additionally, the subset of women taking endocrine therapy had only been on medication for one year, which might limit the additive effect of the medications.

Taken together, the lines of evidence on estrogen and cognition suggest that verbal episodic memory, object-location memory, letter fluency, complex visuomotor attention, speeded manual dexterity, and certain types of verbal working memory are most likely to be sensitive to the effects of estrogen. Other cognitive domains, such as visual memory, category fluency, and confrontational naming appear relatively insensitive to estrogen. The present research examined the effects of endocrine therapy on a range of estrogen-sensitive and estrogen-insensitive measures. Postmenopausal women taking tamoxifen or anastrozole as part of breast cancer treatment and healthy postmenopausal controls completed a comprehensive neuropsychological battery. Postmenopausal women undergoing endocrine therapy were expected to perform more poorly on the estrogen-sensitive measures compared to controls, but no differences were expected on the estrogen-insensitive tasks.

The current research adds to the literature describing the association between estrogen and cognition, and delineates the cognitive side effects of endocrine therapy prescribed in the treatment of estrogen sensitive breast cancer. The neuropsychological health of women taking these medications is an understudied area, but may have an important impact on quality of life and informed choice around the use of this medication. Finally, this research is intended to facilitate the development of improved treatments for breast cancer that will minimize the potential cognitive side effects of the medications used in this prevalent disease.

Methods

Participants

Ethics approval for the study was granted by the University of Saskatchewan Behavioral Ethics Research Board and supported by the provincial Cancer Centre and Council on Aging. Initially, three separate groups of women were recruited for the study: 1) women with estrogen sensitive breast cancer undergoing endocrine therapy (i.e., the endocrine therapy group); 2) women with a history of other forms of cancer who were not undergoing endocrine therapy (i.e., the cancer control group); and, 3) healthy women (i.e., the healthy control group). The cancer groups were recruited through mailed invitations in partnership with a provincial Cancer Registry and invitations distributed by oncologists at a local Cancer Centre. The healthy control group was recruited through invitations mailed in partnership with a local Council on Aging.

To qualify for the study, all women were required to be between the ages of 40 and 80, and to have no previous history of chemotherapy, brain injury or psychiatric disorder. Additional inclusion criteria for the endocrine therapy group included a diagnosis of Stage One estrogen sensitive breast cancer diagnosed within the last one to five years, and endocrine therapy (i.e., tamoxifen or anastrozole) for a minimum of one year. Additional limits for the cancer control group included an early stage non-central nervous system cancer diagnosis within the last one to five years.

A priori exclusionary criteria for all groups included uncorrected visual impairment, nonfluent English, premenopausal status, current hormone replacement use, and/or failure on the cognitive screening instrument. Consequently, nine volunteers were excluded from the study; one volunteer from the endocrine therapy group and six from the healthy women were premenopausal, one volunteer from the healthy group was taking hormone replacement therapy, and one volunteer from the endocrine therapy group had a serious psychiatric illness. The cancer

control group was excluded from the final analysis due to the small number of participants (*n* = 7) and unsuccessful efforts to increase this number.

Sixty-five women were included in the final analyses (28 women undergoing endocrine therapy and 37 healthy post-menopausal women). As described in Table 1, the average age for participants undergoing endocrine therapy was 65.5 years (*SD* = 8.4; ranging from 48 to 79 years) and the average age for healthy participants was 63.9 years (*SD* = 9.3; ranging from 43 to 79 years). Eight-three percent of the women in the endocrine therapy group reported surgery as part of their treatment, and 67% had radiation as part of their treatment. Most women in the endocrine therapy group were taking tamoxifen (78%) as opposed to anastrozole (22%); analyses with and without the women taking anastrozole did not change the pattern of results. For the women taking tamoxifen, 85% were taking a 20 mg dose and 15% were taking a 10 mg dose. All women taking anastrozole were taking a 1 mg dose. For the endocrine therapy group, the average time since diagnosis was 36.6 months (*SD* = 14.5) and the average time since medication was initiated was 34.1 months (*SD* = 14.9) months, ranging from 12 to 56 months. The groups were similar with regard to previous hormone replacement therapy use (i.e., 54% of the treatment group and 42% of the control group had taken HRT in the past). There were 2 left-handed participants who were included in the analyses because each group had one left-hander and their results did not alter the overall findings.

Materials

Health questionnaire. Demographic information (e.g., age, education, body mass index, medications, health problems, and hormone replacement history, etc.) was collected using a standardized self-report health questionnaire.

Sample characteristics, such as demographic information and levels of psychological distress and fatigue, were collected to assess group differences and to rule out potential

confounding variables. Castellon et al. (2004) found that levels of psychological distress and fatigue were higher in women treated for breast cancer, and were negatively associated with cognitive performance. Subjective memory complaints were investigated to determine whether women in the endocrine therapy group report a higher number of complaints compared to controls; past research is equivocal (Jenkins et al., 2004; Paganini-Hill & Clark, 2000). Menopausal symptoms were assessed because tamoxifen produces some side effects that are similar to menopausal symptoms. Body mass index (BMI) was recorded to ensure group equivalency, because BMI is positively correlated with circulating estrogen (McTiernan et al., 2006). Finally, although women in the study did not have a history of chemotherapy, neurotoxicity symptoms were assessed because tamoxifen reportedly can be neurotoxic at higher doses (Chang et al., 1998).

Neuropsychological test battery. Participants completed a standardized neuropsychological test battery and experimental neuropsychological measures. A cognitive screening instrument (Modified Mini-Mental State Examination, 3MS, Ten & Chui, 1987) was included to rule out possible dementia. An estimate of verbal intelligence (Wide Range Achievement Test-3 Reading Subscale, Wilkinson, 1993) was included to assess potential group differences in intellectual ability.

The estrogen-sensitive standardized neuropsychological measures included measures of immediate verbal memory (List Learning and Story Memory; Randolph, 1998), delayed verbal memory (List Recall and Story Recall; Randolph, 1998), complex visuomotor attention (Coding; Randolph, 1998), letter fluency (Controlled Oral Word Association; Benton & Hamsher, 1989), and speeded manual dexterity (Grooved Pegboard; Klove, 1963).

The estrogen-sensitive experimental measures included an object-location memory task (Duff & Hampson, 2001), and a complex verbal working memory task (n-back task; Cohen,

1997; Gevins & Cutillo, 1993). The object-location memory task consisted of a board with 20 flaps covering 10 matching pairs of shapes. The task required participants to uncover the flaps, two at a time, to find all 10 matching pairs of stimuli, by lifting as few flaps as possible. A full description of this experimental measure is found in Duff and Hampson (2001) and procedure was the same as Lejbak et al. (2009). For the n-back task, participants were shown a series of letters presented one at a time each on a computer screen; they were asked to make comparisons between the current letter and the letter presented 2-letters prior by pressing a button if they were the same.

The separate estrogen-insensitive neuropsychological measures included measures of spatial ability (Figure Copy and Line Orientation; Randolph, 1998), confrontation naming (Picture Naming; Randolph, 1998), semantic fluency (Animal Naming; Rosen, 1980), visual memory (Figure Recall; Randolph, 1998), working memory span (Digit Span; Randolph, 1998; Digit Span Backward; Wechsler, 1997), and a spatial version of the n-back task that required participants to make comparisons between the current location of a circle and the location presented 2-locations "back" by pressing a button if they were the same.

Self-Ratings of Psychological Distress, Memory, Fatigue, Neurotoxicity, and Menopausal Symptoms

The Brief Symptom Inventory (BSI), Global Severity Index (GSI) subscale, was used as a standardized measure of psychological distress (Derogatis, 1975). Other self-report measures included a measure of fatigue (Epworth Sleepiness Scale; Johns, 1991), subjective memory complaints (Cognitive Failures Questionnaire; Broadbent, Cooper, Fitzgerald, & Parkes, 1982), neurotoxicity symptoms (Arbuthnott & Crossley, unpublished) and menopause symptoms (The Menopause Questionnaire: Symptom Analysis; North American Menopause Society, unpublished). The neurotoxicity measure assessed 19 symptoms presumed to relate to

neurotoxicity (e.g., dizziness, nausea, fatigue, etc.) using a 5-point scale. The menopause measure assessed 33 symptoms presumed to relate to menopause (i.e.., vasomotor, psychological, urinary, sexual and pain symptoms) using a 5-point scale.

Apparatus

The object-location experimental task (Duff & Hampson, 2001) was made of white foam board (36 cm wide x 45 cm long), and had twenty foam board flaps (4.5 wide x 8.0 cm long) to hide the stimuli (3 cm). The stimuli were laminated black ink shapes on white paper. The experimental n-back task was created using the psychology experiment computer program E-Prime Version 1.2 and performed on a personal computer laptop with a standard 15 inch computer monitor. For the verbal version, the letters were presented at 2500 ms intervals in Courier New font with a font size of 72. In total, all 20 consonants were used (vowels were excluded). For the spatial version, locations were represented by a 3 cm circle that moved across 20 different locations. Participants pressed a "white button" (i.e., a sticker placed over the letter "n" on the keyboard) when a letter or separate location matched.

Procedure

After providing informed consent, participants were tested individually in a private room. All participants completed the same assessment, starting with the demographic and health questionnaire, followed by the cognitive screen and neuropsychological measures (i.e., the Repeatable Battery for the Assessment of Neuropsychological Status, verbal fluency measures, Grooved Pegboard, the object-location memory measure, and the n-back measure), and ending with the self-report questionnaires. All nonexperimental measures were administered according to published standardized protocols. Once participants completed the assessment, they were debriefed about the nature of the study and given an opportunity to ask questions.

Statistical Analyses

All analyses were performed using the Statistical Program for Social Sciences (SPSS) version 14.0. Sample characteristics (e.g., age, education, psychological distress, body mass index), self-report questionnaires, the cognitive screen, and the estimate of verbal intelligence were analyzed using a series of two-tailed, independent samples t-tests with Group (endocrine therapy vs healthy) as the independent factor in all analyses. As described below, some of these measures served as covariates in subsequent analyses of significant group differences.

The analysis for the estrogen-sensitive tasks was a one-way multivariate analysis of variance (MANOVA) with Group (endocrine therapy vs healthy) as the independent variable and List Learning, Story Memory, List Recall, Story Recall, Object-Location Memory, Complex Visuomotor Attention, Letter Fluency, Complex Verbal Working Memory, and Speeded Manual Dexterity as the dependent variables. Pillai's Trace was used as the *F* statistic for the MANOVA. Results were considered significant at a *p* value of $<.05$.

One-way between-subjects univariate ANOVAs were run for the estrogen-insensitive neuropsychological measures. Group (endocrine therapy vs healthy) was the independent variable and Figure Copy, Line Orientation, Semantic Fluency, Confrontational Naming, Visual Delayed Memory, Digit Forward, Digit Backward, and Complex Spatial Working Memory were the dependent variables. Bonferroni corrections were applied to test significance given the high number of analyses.

Results

Data Cleaning

For separate variables with less than 5% missing data, missing data points were replaced using the group mean. In total, 11 missing data points out of a possible 1584 data points were replaced (i.e., .01%). For the n-back task, with 12% missing data, participants with missing data points were excluded and the measure was analyzed separately using an ANOVA with 26

participants in the endocrine therapy group and 31 in the control group. Using a criterion of 3.3 standard deviations, 12 univariate outlier data points were identified across all measures (i.e., .01%). Univariate outliers were tightened to 3.3 standard deviations from the group mean. Using the same cutoff, no multivariate outlier cases were discovered.

Sample Characteristics

Table 1 contains the means, standard deviations, and test statistics for sample characteristics, self-report questionnaires, cognitive screening scores, and estimates of verbal ability. Given the high number of analyses, a conservative significance value ($p < .01$) was applied to reduce the likelihood of a Type I error. Independent samples t-tests demonstrated that the groups did not differ with regard to age, education, body mass index, number of medications, number of health problems, neurotoxicity symptoms, sleepiness, menopause symptoms, subjective memory complaints, cognitive screen scores, or estimated verbal ability. A significant group difference was detected, however, on the measure of psychological distress ($p < .01$); the endocrine therapy group reported a higher level of global psychological distress compared to controls. The menopause measure approached significance ($p = .06$) but it did not survive Bonferonni corrections given the number of analyses.

Analyses of Estrogen-Sensitive Neuropsychological Measures

All assumptions for MANOVA were met. A one-way MANOVA was run with Group (endocrine therapy vs healthy) as the fixed factor and the estrogen-sensitive tasks (List Learning, Story Memory, List Recall, Story Recall, Object-Location Memory, Complex Visuomotor Attention, Letter Fluency, and Speeded Manual Dexterity) as the dependent variables. The MANOVA was significant for Group, $F(8, 56) = 2.40$, $p = .03$; the effect size was considered moderate ($f^2 = 0.29$; Cohen, 1992). The ANOVA for Complex Verbal Working Memory did not reach significance, $F(1, 55) = 1.49$, $p = .23$.

INSERT TABLE 2 ABOUT HERE

As described in Table 2, univariate ANOVAs revealed significant group differences on measures of Complex Visuomotor Attention, F (1, 63) = 7.67, p = .01, Cohen's d = .69, Letter Fluency, F (1, 63) = 5.25, p = .03, Cohen's d = .58, and Speeded Manual Dexterity, F (1, 63) = 12.71, p < .01, Cohen's d = .87, with healthy participants performing better than participants undergoing endocrine therapy. The two groups did not differ significantly on any of the memory measures.

Because the GSI of the Brief Symptom Inventory was significantly higher for the endocrine therapy group compared to the healthy participants, a MANCOVA was run using this measure of psychological distress as a covariate. The MANCOVA remained significant for group, F (8, 55) = 2.83, p = .04, while the measure of psychological distress (GSI) did not reach significance, F (8, 55) = 1.55, p = .16. Although average age was not significantly different between the two groups, age was used as a covariate to control for the wide age range of participants. The covariate of age was significant, F (8, 55) = 6.84, p <.01, and the overall MANCOVA remained significant, F (8, 55) = 2.82, p =.01. For both covariates, the same measures (i.e., Complex Visuomotor Attention, Letter Fluency, and Speeded Manual Dexterity) remained significant for the univariate analyses.

Given that many studies examining the cognitive effects of cancer treatments have found that only a subgroup of treated patients is affected, we analyzed the data at an individual level to supplement the group level analyses. Participants' scores were coded into impaired versus unimpaired using the criterion of 1.5 standard deviations below the control group mean as a cut-off for impaired performance. Ingraham and Aiken's (1996) methodology was used to determine the number of tests needed to show an overall impairment on the estrogen-sensitive measures at a significance level of p < .05; using this criteria, at least three out of the nine measures needed to

be impaired. The frequency of individuals with impairments for each of the groups was then examined on the individual measures as well as for the overall estrogen-sensitive battery. Using chi square analyses, no significant group differences at $p < .05$ were found on any of the individual measures or for the estrogen-sensitive battery.

Similar analyses were performed on the subjective measures using a criterion of two impaired scores at 1.5 standard deviations above the control group mean (higher scores equaled a higher number of symptoms). Significant group differences for overall impairment on the subjective measures were not found, but more individuals in the endocrine therapy group reported impairment on the measure of psychological distress, χ^2 (1, N= 65) = 4.93, p = .03, and the menopause measure, χ^2 (1, N= 65) = 6.95, p = .01, which is consistent with the group comparisons described earlier.

Analyses of Estrogen-Insensitive Neuropsychological Measures

None of the group comparisons using the estrogen-insensitive measures reached significance. Although Semantic Fluency approached significance, F (1, 63) = 3.62, p = .06, it did not remain so once the Bonferroni correction (i.e., p<.01) was applied. Table 2 contains the means, standard deviations, and effect sizes for the estrogen-insensitive measures.

Discussion

The hypotheses for the present study were partially supported. As expected, postmenopausal women undergoing endocrine therapy performed more poorly on measures of letter fluency, complex visuomotor attention, and speeded manual dexterity compared to controls of similar age, education, and ability; using Cohen's *d* (Cohen, 1988) the effect sizes were medium for letter fluency and complex visuomotor attention, and large for speeded manual dexterity. Unexpectedly, the groups did not differ on measures of immediate and delayed verbal memory, object-location memory, or complex verbal working memory. These findings were

robust to analyses that controlled for the higher level of psychological distress in the endocrine therapy group. As expected, the neuropsychological measures predicted to be relatively insensitive to estrogen (i.e., spatial ability, visual memory, confrontational naming, and working memory span) did not differ between the groups; although semantic fluency approached significance in favor of controls, the trend did not remain after a significance correction for multiple analyses.

The finding that women taking endocrine therapy generated fewer words on letter fluency compared to controls provides further support for the influence of estrogen on this task and is consistent with the sex-related differences research (e.g., Crossley et al., 1998; Loonstra et al., 2001; Weiss et al., 2006) and with some of the estrogen supplementation research (Szklo et al., 1996). Recent studies have demonstrated sex-related differences in strategy use on verbal fluency tasks. For example, Weiss et al. (2006) found that women balance clustering and switching on letter fluency tasks more than men, which appears to be the best strategy for this task. Lanting, Haugrud and Crossley (2009) found that females produced smaller clusters of words on letter and semantic fluency, and switched more frequently on semantic fluency, regardless of age. It would be interesting to know whether women undergoing endocrine therapy use less efficient strategies, leading to poorer performance. Related to this question, further investigation into retrieval processes and the phonemic storage capacity may elucidate the reasons for the observed performance differences. Testing to exhaustion of the phonemic store and including other retrieval measures may shed some light on which processes are most affected.

The finding that women undergoing endocrine therapy were slower on a measure of complex visuomotor attention compared to controls is consistent with a female advantage (e.g., Snow & Weinstock, 1990) and an estrogen suppression/estrogen depletion disadvantage (Jenkins

et al., 2004; Collins et al., 2009) for these types of tasks. Jenkins et al. (2008) did not include a symbol decoding task in their study on anastrazole, making it difficult to compare findings. Interestingly, Lezak (2004) noted that symbol-number decoding tasks are the most sensitive, albeit non-specific measures of brain insult; this measure may be detecting subtle changes in brain functioning as a result of the medication. Given the sensitivity of symbol-digit decoding tasks to detect subtle changes in neural functioning, evidence for the influence of estrogen on symbol-digit decoding tasks, and Zec and Trivedi's (2002) finding that visual search tasks are the most sensitive non-memory measures, future studies may want to include both symbol-digit decoding and visual search measures.

As expected, women undergoing endocrine therapy took longer than controls to complete a measure of speeded manual dexterity. This finding is consistent with the literature on a female advantage (Bryden & Roy, 2005; Schmidt et al., 2000) and the smaller body of literature on an estrogen supplementation advantage (Schmidt et al., 1996) for speeded manual dexterity tasks. Although Stewart, Collins, Mackenzie, Tomiak, Verma and Bielajew (2008) found that women undergoing hormonal therapy for breast cancer performed similarly on pre- and post-tests, their baseline measure might have been affected by the stress of a recent diagnosis and effects of anesthesia from recent surgery. Additionally, women in their study had been taking endocrine therapy for a shorter duration compared to women in our study (i.e., an average of less than one year compared to three years); an additive effect of the medications cannot be ruled out as an explanation for the differences. We did not assess simpler measures of motor speed, such as finger tapping rates, so are unable to comment on whether the effect is a result of manual dexterity, motor speed, or a combination of the two. Interestingly, all of the measures that produced a significant group difference were timed (including the one measure presumed to be estrogen-insensitive that approached significance), which suggests that processing speed may be

an important factor in conceptualizing the observed effects. Notably, the relatively poorer processing speed in the treatment group speed is consistent with Collins et al. (2009) finding of an overall effect for processing speed, using three different speeded measures. Another way of conceptualizing the observed effects is that they all involve frontal lobe functioning, which is consistent with the pattern of decreased frontal lobe activity in women taking tamoxifen as observed by Eberling et al. (2004).

Unexpectedly, the two groups did not differ significantly on any of the verbal memory tasks. Our lack of effect for verbal episodic memory is in contrast to the wide body of literature reporting a female advantage (e.g., Kramer et al., 1988; Norman et al., 2000), an estrogen supplement advantage (Zec & Trivedi, 2002), and an anti-estrogen/ estrogen depletion disadvantage (Jenkins et al., 2004; Collins et al., 2009), particularly for paragraph recall tasks. Although the measures we used are typically sensitive to the female advantage for verbal episodic memory (Beatty, Mold & Gontkovsky, 2003), we observed a ceiling effect for approximately 33% of all participants by the final learning trials on both list learning and story learning, and for approximately 16% of participants on the delayed story measure. These results might have reduced our sensitivity to detect differences. Our lack of effect, however, is consistent with Jenkins et al. (2008), who found no differences on any verbal episodic memory measures in women taking anastrozole who served as their own controls.

Our failure to find group differences on an object-location memory task also contrasts the female advantage (e.g., Duff & Hampson, 2001; Lejbak et al., 2009) and estrogen supplementation advantage found by others (e.g., Hampson & Duff, 2000). To our knowledge, we are the first to use the object-location memory measure in a group that includes older adults; it is possible that the female and estrogen advantage decline with age, making this task a less

sensitive measure for older adults. Future studies are needed to investigate the interaction between sex and age for object-location memory measures.

The validity of the complex verbal working memory measure (i.e., the n-back task) is questionable because approximately 20% of participants in both groups were either unable to complete the task or scored below chance. Women unable to complete the task tended to be older and to score lower on measures of verbal intellectual ability. The high degree of difficulty of the n-back task also was observed by Lejbak, Crossley and Vrbancic (in review) with some younger participants, who again tended to score lower on verbal ability measures. This suggests that ability might be a relatively more important factor than age or sex in determining who will have difficulty completing the task. Future studies will benefit from verbal working memory measures that are less dependent on high levels of intellectual ability.

Notably, the results of this study, which found a treatment effect for complex visuospatial attention, letter fluency, and speeded motor dexterity, differ from recent prospective studies showing no effect of endocrine therapy on cognition (i.e., Hermelink et al., 2008; Jenkins et al., 2008; Stewart et al., 2008). Our study differs from the prospective studies in important ways that could account for some of the observed discrepancies. Women in our study were undergoing hormonal therapy for a longer period of time (i.e., an average of three years) compared to the prospective studies listed above (i.e., six months, two years, and one year, respectively). It will be important for future studies to empirically test the effect of duration on cognitive performance in women undergoing endocrine therapy. Furthermore, our sample included middle aged and older adults, compared to the prospective studies that included only middle aged women in their samples. It is possible that older women are more sensitive to the effect of estrogen therapies; age-related differential drug sensitivities are reported frequently in aging research (Berg & Dellasega, 1996; Grossberg & Grossberg, 1998).

More research is needed regarding the action of tamoxifen and anastrozole at receptor sites, and may help elucidate some of the cognitive effects associated with these medications. Presumably, tamoxifen and anastrozole exert physiological effects beyond suppressing the action of estrogen in the central nervous system of postmenopausal women. For example, anastrozole prevents the conversion of androstenedione to estrone, which not only suppresses the action of estrogen but will have additional effects on the sensitivity of receptors, production of other hormones, action of other hormones, and so on. At present, we do not know enough about the action of estrogen and estradiol at specific receptor sites in the central nervous system to determine the full effects. Related, the idea that estrogen suppression should influence measures similar to those affected by estrogen supplementation might be flawed. The absolute volume change of estrogen in the bloodstream is greater when supplementing compared to suppressing, and they also work on different estrogens. Estrogen supplementation typically involves increasing estradiol, whereas estrogen suppression in postmenopausal women typically involves suppressing estrone, the most prevalent, yet less powerful, estrogen in postmenopausal women. More research is needed to examine the action estradiol and estrone supplementation and suppression in the central nervous system. Because tamoxifen is a SERM, the effects on brain estrogen receptors might be even more complicated.

There are several limitations to the current study. We had difficulty recruiting participants for our cancer control group, because the pool of participants within the study region who met criteria for the study was small. Without a cancer control group, we are unable to determine whether the observed effects are due to estrogen suppression as opposed to a nonspecific effect associated with a diagnosis of cancer. Furthermore, we did not have a baseline measure of cognitive functioning. Future research that recruits women prior to initiating endocrine therapy so that they can serve as their own controls will help to eliminate some of the

potential confounds associated with cross-sectional studies. In addition to assessing women before they begin endocrine therapy, it would be interesting to know whether cognitive changes persist after women discontinue the medication. We did not include premenopausal women in the study due to difficulty with recruitment; it is possible that premenopausal women would demonstrate more pronounced cognitive effects compared to postmenopausal women, since total estrogen depletion from the medications would be greater in premenopausal women. Another limitation to this study is that we combined women taking tamoxifen with women taking anastrozole. Although other researchers have combined these estrogen therapies (e.g., Jenkins et al. 2004; Collins et al., 2009), we recognize that the two medications work in different ways, limiting the specificity of the results.

Finally, the clinical relevance of the findings should be considered. Interestingly, we did not find that women undergoing endocrine therapy reported more memory problems compared to healthy controls. This contrasts observational reports from oncologists and the research of Paganini-Hill and Clark (2000), but is consistent with Jenkins et al. (2004). We did find, however, that level of psychological distress was significantly higher in women undergoing endocrine therapy. This finding is not surprising given the psychosocial impact of the diagnosis, and might even support a biological role for estrogen in emotional functioning. It should be noted, however, that although the difference in psychological distress reached statistical significance, none of the women in the current study were in the clinical range of psychological distress. Lastly, the clinical significance of the differences in cognition should be considered. It is important to note that although we found statistically significant group differences, none of the women from either group would be considered cognitively impaired, which may reassure women taking the medication.

Table 1.

Endocrine Therapy and Healthy Control Group Means (SD) and Test Statistics for Demographic, Health, and Self-Report Measures.

	Group		
Characteristic	Endocrine Therapy Group Mean (SD)	Control Group Mean (SD)	p value
Age	65.5 (8.4)	63.9 (9.3)	=.48
Education	14.0 (2.8)	14.9 (2.6)	=.14
Cognitive Screen [a]	97.6 (2.5)	98.1 (2.1)	=.48
Ability Estimate [b]	47.1 (4.4)	47.3 (4.0)	=.85
Body Mass Index [c]	26.6 (4.9)	25.3 (4.1)	=.24
Psychological Distress [d]	56.1 (6.8)	49.8 (6.9)	<.01
Neurotoxicity [e]	6.4 (5.9)	5.0 (4.0)	=.28
Fatigue [f]	6.7 (4.3)	6.4 (3.6)	=.76
Self-Report Memory [g]	32.3 (12.9)	32.9 (11.5)	=.84
Menopause Symptoms [h]	49.0 (12.1)	44.1 (7.8)	=.06

[a] The 3MS is scored out of 100 points with scores below 80 indicating possible dementia.

[b] The WRAT-3 Reading score is the number of each word correctly pronounced (and additional 15 points are added to this total) for a maximum score of 57.

[c] Body mass index was calculated using the formula: BMI = weight (kg)/height^2

[d] The Brief Symptom Inventory-Global Severity Index scores were converted to t-scores using "outpatient women" as the normative sample.

[e] Neurotoxicity measure scores are summed across 19 items; scores range 0 to 76.

[f]. The Epworth Sleepiness Scale scores are summed across 8 items; scores range from 0 to 24.

[g]. The Cognitive Failures Questionnaire scores are summed across 25 items; scores range from 0 to 100.

[h]. Menopause Measure scores are summed across 33 items and range from 33 to 165.

Table 2.

Endocrine Therapy and Healthy Control Group Means (SD) and Effect Sizes for the Estrogen-Sensitive Neuropsychological Measures

Neuropsychological Measure	Group: Endocrine Therapy Group Mean (SD)	Group: Control Group Mean (SD)	*p*-value	Cohen's *d*
List Learning [a]	29.0 (5.1)	30.3 (3.8)	=.24	0.29
List Recall [b]	7.1 (2.2)	6.8 (2.2)	=.58	0.14
Story Memory [c]	17.1 (3.6)	18.4 (3.3)	=.15	0.38
Story Recall [d]	9.0 (2.3)	9.7 (2.1)	=.23	0.32
Coding [e]	42.9 (9.5)	49.3 (9.2)	=.01	0.69*
Letter Fluency [f]	40.0 (10.8)	44.3 (11.2)	=.03	0.58*
Object-Location [g]	47.5 (21.1)	44.4 (20.0)	=.55	0.15
Grooved Pegboard [h]	80.9 (17.1)	67.76 (12.7)	<.01	0.87*
Verbal N-Back [i]	119.9 (9.7)	123.0 (9.5)	=.23	0.32

* $p \leq .05$

[a] The List Learning score is the number of words correctly remembered over 4 trials, for a maximum raw score of 40.

[b] The List Recall score is the total number of words remembered after a delay for a maximum raw score of 10.

[c] The Story Memory score is the number of phrases correctly remembered over two trials, for a maximum raw score of 24

[d] The Story Recall score is the total number of phrases remembered after a delay, for a maximum raw score of 12.

[e] The Coding score is the number of correct decoded number-symbol pairs in 90 seconds, for a maximum raw score of 89.

[f] The Controlled Oral Word Association Test score is the total number of novel words generated from the target letters "c", "f", and "l" over three 1-minute trials, excluding proper names and variants of the same word (e.g., "frank" and "frankly").

[g] The Object Location Memory measure score is the number of errors (i.e., searching an already viewed, non-matching image).

[h] The Grooved Pegboard score was the time to completion in seconds for placing all 25 pegs in the holes using the dominant hand.

[I] The n-back score was the number of correct responses for a maximum score of 140, and was based on a sample of 26 in the endocrine therapy group and 31 in the healthy control group.

Table 3

Endocrine Therapy and Healthy Control Group Means, Standard Deviations, and Effect Sizes for the Estrogen-Insensitive Measures

Neuropsychological Measure	Group: Endocrine Therapy Group Mean (SD)	Group: Control Group Mean (SD)	*p*-value	Cohen's *d*
Figure Copy [a]	16.93 (2.16)	17.16 (2.18)	=.67	0.11
Line Orientation [b]	16.68 (2.75)	17.76 (2.35)	=.09	0.42
Animal Naming [c]	19.29 (4.84)	21.84 (5.71)	=.06	0.48
Picture Naming [d]	9.71 (0.46)	9.86 (0.35)	=.14	0.35
Figure Recall [e]	12.39 (3.02)	13.08 (3.70)	=.43	0.20
Spatial N-Back [f]	121.35 (10.68)	122.23 (11.54)	=.76	0.08

[a] The Figure Copy score was the number of correct drawing (1 point each) and correct placement (1 point each) of the elements copied from a figure for a maximum score of 20.

[b] The Line Orientation was the total number of correct judgments about lines for a maximum score of 20.

[c] The Animal Naming score was the number of novel animals generated over a 1-minute trial.

[d] The Picture Naming score was the number of correctly identified pictures for a maximum score of 10.

[e] The Figure Recall score was the number of correct drawing (1 point each) and correct placement (1 point each) of the elements remembered from a figure for a maximum score of 20.

[f] The n-back score was the number of correct responses for a maximum score of 140, and was based on a sample of 26 in the endocrine therapy group and 31 in the healthy control group.

General Discussion

The three studies comprising this doctoral dissertation investigated the effects of sex and of estrogen suppression on working memory and other neuropsychological functions. Research has demonstrated a female advantage for certain working memory measures, including Duff & Hampson's (2001) object-location task that has a strong working memory component, and the verbal n-back task (Speck et al., 2000). Because Duff and Hampson's (2001) measure used verbalizable stimuli (i.e., colours and shapes) and Speck et al.'s (2000) study included only a verbal (i.e., letters) condition, it was unknown whether the female advantage was robust to difficult-to-verbalize stimuli and other working memory domains (e.g., object, spatial). This distinction is important given the potential verbal contribution to the task, for which females typically show an advantage (Bolla et al., 1999; Crossley et al., 1997; Hedges & Nowells, 1995; Stanley et al., 1992; Weiss et al., 2006), and the findings that other memory systems (e.g., episodic memory, object-location memory) typically demonstrate a female advantage for verbal material only (Choi & L'Hirondelle, 2005; Lewin et al., 2001). Finally, the effect of estrogen suppression on Duff and Hampson's (2001) measure and the n-back task have not been studied in postmenopausal females despite findings of performance facilitation with estrogen supplementation (Hampson & Duff, 2001; Keenan et al., 2001) and performance decline with estrogen suppression in premenopausal females on the n-back task (Grigorova et al., 2006).

Studies 1 and 2 examined whether the female advantage for certain measures of verbal working memory was robust to non-verbal stimuli in young adults, and Study 3 investigated the effect of estrogen suppression in middle-aged and older females taking endocrine therapy (i.e., estrogen suppression with either tamoxifen or anastrozole) for breast cancer treatment on working memory and other estrogen-sensitive measures. Study 1 replicated and extended Duff and Hampson's (2001) findings by manipulating the verbalilzability of the stimuli (i.e., common

objects, geometric shapes, and novel shapes) on the object-location working memory measure, and a computerized version of the measure was also created for ease of administration and scoring. The hypotheses for Study 1 were supported. Females made fewer working memory errors than males on the object-location working memory measure regardless of the degree of verbalizability of the stimuli or mode of presentation (manual vs computer). Notably, the effect size for accuracy was "large" (Cohen, 1988) and consistent with Duff and Hampson's (2001) and McBurney et al.'s (1997) effect sizes. Interestingly, females were significantly faster on the manual version of the measure whereas males were significantly faster on the computer version of the measure.

Study 2 examined sex-related differences on verbal, spatial, and object versions of the n-back working memory task. A secondary goal of Study 2 was to create a measure that was less confounded by degree of difficulty than previous measures. The hypotheses for Study 2 were partially supported. Not unexpectedly, males performed significantly better than females on the spatial version of the task; however, contrary to the hypotheses, there was no sex effect for the verbal version of the task and males actually outperformed females on the object version of the task. Regarding reaction time, males were faster than females only when responding to the spatial version of the task. Study 2 also investigated task equivalency for the different versions of the n-back task. Most often, spatial versions of the task are much easier than verbal versions (Postle et al., 2005); typically only 9 locations are used in spatial versions, making it a relatively easy task compared to the verbal version, which uses up to 20 letters. In the present study, the spatial version included 20 locations, the verbal version included 20 letters, and the object version included 20 objects. Task equivalency was established for females but not males, as males performed significantly worse on the verbal version compared to the spatial and object

version. This suggests that although task version equivalency is likely not attainable due to the sex-related differences, it is less confounded than reported in previous studies.

Study 3 investigated the effect of estrogen suppression in middle-aged and older females taking endocrine therapy (i.e., tamoxifen or anastrozole) as part of breast cancer treatment on estrogen-sensitive neurocognitive measures (i.e., measures that show a female advantage, performance facilitation with estrogen supplementation, and/or performance debilitation with estrogen suppression). The hypotheses for Study 3 were also partially supported. As expected, middle-age and older adult females undergoing endocrine therapy did not perform as well as healthy age and education-matched controls on certain estrogen-sensitive measures (i.e., complex visuomotor attention, speeded manual dexterity, and letter fluency), and no group differences were found on the estrogen-insensitive measures (although semantic fluency unexpectedly approached significance in favor of controls, the trend did not remain after a significance correction for multiple analyses). Unexpectedly, however, group differences were not observed for the working memory measures used in Studies 1 and 2 or the other estrogen-sensitive measures (i.e., immediate and delayed verbal episodic memory). Interestingly, a common denominator among the measures that showed a treatment effect is processing speed; further investigation of processing speed as an underlying factor contributing to group differences is warranted.

Overall, the findings of a female advantage for object-location working memory from Study 1 supports the growing body of literature that demonstrates a female advantage for object-location memory that has a significant working memory component (Duff & Hampson, 2001; McBurney et al., 1997), and object-location memory with fewer working memory demands (Eals & Silverman, 1994; Silverman & Eals, 1992; Sykes-Tottenham, Saucier, Elias, & Gutwin, 2003). It also demonstrates that the female advantage is evident regardless of the verbalizability of the

stimuli, which is consistent with Eals and Silverman (1994), who found that the female advantage was robust to abstract stimuli, and in contrast to the findings of Choi and L'Hirondelle's (2005), who found a male advantage when the verbal component of their object-location memory task was removed. The findings from this study also show that Duff and Hampson's (2001) object-location working memory task can be adapted for computer use, although it becomes an easier task for both sexes, making it less sensitive to sex effects. Given that the female advantage was consistent across conditions, Study 1 also provides support for the hypothesis that the female advantage is due to central executive processing (Duff & Hampson, 2001) as opposed to phonological processing, because participants would not have been as easily able to verbally rehearse the abstract stimuli.

Regarding Study 2, the lack of a female advantage on the verbal version of this working memory task is in contrast to Speck et al. (2000), but is consistent with Nagel et al.'s (2007) and Goldstein et al. (2005). Notably, both Speck et al. (2000) and Goldstein et al. (2005) demonstrated sex-related differences in neural activation during the task. The finding of a male advantage for the spatial n-back is also inconsistent with Nagel et al.'s (2007) non-fMRI n-back study. There are differences between Study 2 and Nagel et al.'s (2007) study regarding the spatial n-back task which may account for some of the discrepant findings; in Nagel et al.'s (2007) study, stimuli were presented more slowly, the protocol was less demanding, and spatial and verbal materials were confounded, adding an additional requirement of "inhibition" to the task. Notably, the male advantage for the spatial n-back found in Study 2 is consistent with reports of a male advantage for spatial span tasks (Orsini et al., 2003). Study 2 was the first to investigate sex-related differences on an object version of the n-back task; studies further exploring the male advantage are needed.

The finding of task equivalency for females but not males across the different versions of the n-back task in Study 2 contributes to the debate on domain specificity in working memory. There is some question as to whether working memory is a domain-specific (i.e., verbal, spatial, object) process (Owen, Lee & Williams, 2000). Postle et al. (2000) used fMRI to investigate spatial and object (Attneave shapes) versions of the n-back task and found that they could not differentiate between domains for the neural correlates. Owen et al. (2005) also found little differentiation among domains (i.e., letters, objects, locations) with regard to neural correlates. Study 2's behavioral data supports the idea that working memory is not domain specific, but only for females, who performed similarly across the n-back tasks and the object-location measure versions. Future research could further investigate the domain specificity of working memory with regard to sex-related differences by investigating other working memory measures that can be manipulated by domain.

The results from Study 3 can also be placed within the context of the literature in this area. The finding that women taking endocrine therapy generated fewer words on letter fluency, were slower on a measure of complex visuomotor attention, and were slower on a measure of speeded manual dexterity compared to controls is consistent with the literature on sex-related differences (e.g., Bryden & Roy, 2005; Crossley et al., 1998; Loonstra et al., 2001; Schmidt et al., 2000; Snow & Weinstock, 1990; Weiss et al., 2006), estrogen supplementation (Schmidt et al., 1996; Szklo et al., 1996) and estrogen suppression (Jenkins et al., 2004). The lack of treatment effect for immediate and delayed verbal episodic memory measures is consistent with Jenkins at al. (2008) and Stewart et al. (2008) but inconsistent with Jenkins et al. (2004).

Notably, the null findings in Study 3 for the experimental working memory measures used in Studies 1 and 2 is inconsistent with some of the literature. The lack of a treatment effect for the object-location working memory measure in Study 3 is inconsistent with and Hampson

and Duff's (2000) finding that women taking estrogen supplementation performed better than controls on their object-location working memory task, and is also inconsistent with Study 1, which demonstrated that the measure is sensitive to the female advantage. The lack of effect for the n-back task in Study 3 is inconsistent with research demonstrating an influence of estrogen on these measures. Grigorova et al. (2006) demonstrated that premenopausal women taking estrogen suppressing medication as treatment for gynecological disorders had poorer performance compared to controls on the verbal and abstract shape version of the n-back task, and Keenan et al. (2001) showed that postmenopausal women taking estrogen supplementation performed better than controls on an auditory n-back task. The lack of treatment effect for the n-back task in Study 3, however, is consistent with the lack of female advantage found in Study 2. Evidently, further research is needed to determine the reasons for the discrepant findings between the experimental working memory measures used in Study 3 and the literature in the area.

Taken together, Studies 1 and 2 demonstrate that certain working memory measures are sensitive to sex, although not in a uniform manner. With regard to working memory theory, the lack of a female advantage for the n-back task, which presumably engages central executive processes (Baddeley, 2003), is inconsistent with Duff and Hampson's (2001) assertion that the female advantage for the object-location working memory task is due to central executive processes. These inconsistencies suggest that if both tasks are engaging the central executive, they are engaging different executive components, or different working memory components altogether. It is possible that the object-location memory task, with its multirepresentational nature and episodic element, might activate Baddeley's (2000) episodic buffer, and that this element is driving the female advantage on the object-location working memory measure as opposed to the central executive per se. The male advantage for the spatial and object n-back task may be more germane to central executive processing, as it does fit with Cattaneo et al.

(2006), who found that males performed better than females on a visuospatial working memory measure known to engage the central executive. Further studies are needed to test sex-related differences and their role in the working memory model directly.

There are several possible explanations for the apparent contradictory findings between Studies1 and 2. The measures in Studies 1 and 2 might not have been measuring the same construct; perhaps Duff and Hampson's (2001) object-location working memory measure is simply an object-location memory measure. Given the high number of studies showing a female advantage for object-location memory tasks (Eals & Silverman, 1994; McBurney et al., 1997; Sykes-Tottenham et al., 2003; Silverman & Eals, 1992; Voyer et al., 2007) and few studies showing a female advantage for working memory measures, the simplest explanation might be that object-location memory is producing the sex effect. Analyses of the neural correlates of the tasks could also help delineate the similarities and differences between the tasks. There is ample evidence for the neural correlates of the n-back task; a meta-analysis demonstrated consistent patterns involving lateral premotor cortex; dorsal cingulate and medial premotor cortex; dorsolateral and ventrolateral prefrontal cortex; frontal poles; and medial and lateral posterior parietal cortex (Owen, McMillan, Laird, & Bullmore, 2005). The only fMRI study of Duff and Hampson's object-location working memory measure (Levine, Mohamed, & Platek, 2005) demonstrates activation in superior temporal lobe, as well as many other sex-related differences in activation, but it did not activate the dorsolateral PFC consistently, perhaps suggesting it is a more complex and less well defined working memory measure. Future studies might differentiate between the working memory and object-location memory components of the task, perhaps by manipulating the working memory component (e.g., keep the flaps open).

With regard to Study 3, there are several possible reasons for the contradictory findings among Study 3, the previous studies, and the literature. In the present research, the procedure for

the object-location memory measure was modified slightly from Duff and Hampson (2001) and Hampson and Duff (2000), as only one trial was presented as opposed to three learning trials followed by a delay in an effort to make it more of a working memory measure and less of an episodic memory measure. This same procedure, however, was also used in Study 1 and did not affect its ability to detect a female advantage of the same magnitude as Duff and Hampson (2001); performance on the first trial in Study 1 was similar to Duff and Hampson's first trial. Hampson and Duff (2000) did not report trials separately when investigating the effects of estrogen supplementation on the task; perhaps later trials were responsible for the effect as opposed to the first trial.

The lack of a treatment effect for the n-back task in Study 3 might in part be due to the validity of the measure. As in Study 2, a high percentage of the participants were unable to complete the task, despite slowing the rate of presentation from 1s to 2.5 s. In contrast to Study 2, participants did not have a high number of non-responses; rather, a subset of mostly older participants was simply unable to comprehend the instructions and this did not complete the task. Thus, the n-back task is a difficult task, particularly for older adults. Other researchers have reported loss of older participants who could not complete demanding working memory measures (Salat, Kaye, & Janowsky, 2002). Future studies could examine the effect of estrogen suppression on less demanding forms of the n-back task (e.g., slow the rate of presentation) or use an auditory version to reduce the possible confound of computer literacy.

Differences in age are also potential explanations for the differences between Study 3 and the literature. Attempts to recruit younger females and premenopausal females were unsuccessful in Study 3, perhaps due to the aggressive treatment offered to younger women with breast cancer (i.e., chemotherapy), which excluded them from this research. Instead, a higher age range was added to Study 3 in an attempt to increase the number of participants, resulting in a middle-age

group and an older group. In contrast, Hampson and Duff (2000) and Keenan et al. (2001) included only middle-aged women, and Grigova et al. (2006) included only young women. Although the n-back task has been used with older adults, to our knowledge, Duff and Hampson's (2001) object-location memory measure has not been examined in older adults. It is well known that variability increases in older participants, which may have limited our power to detect group differences. It would be interesting to know whether the sex-related differences observed on the object-location memory measure and n-back task occur in older adults; given the sex-related difference in PFC decline (i.e., females do not show a decline whereas males do; Cowell et al., 1994; DeCarli et al., 2005; Gur et al., 2002), it is possible that the female advantage for the object-location memory measure will increase while the male advantage for the spatial and object n-back task will decrease.

The fact that menopausal status is confounded with age in females may also explain some of the findings in Study 3. Grigorova et al.'s (2006) sample, which experienced adverse effects of working memory on the n-back task after taking estrogen suppressing medication, was not only younger, but also premenopausal. Suppressing estrogen in premenopausal women may be more deleterious than suppressing estrogen in postmenopausal women due to the fact that estradiol levels are still high. Furthermore, estrone, the primary estrogen in postmenopausal women, is not as potent as estradiol and has not been shown to have a large effect on cognitive functioning. Unfortunately, attempts to recruit premenopausal females for Study 3 were unsuccessful. Future studies could examine the effect of estrogen suppression (e.g., leuprolide acetate depot, tamoxifen) in premenopausal women on Duff and Hampson's object-location working memory measure and other estrogen-sensitive neuropsychological measures.

In Study 3, the logic behind the hypothesis that estrogen suppression should influence measures sensitive to the female advantage or to estrogen supplementation might be flawed. In

other words, the facilitation of a neuropsychological task with estrogen supplementation does not necessarily mean that the suppression of estrogen will lead to poorer performance on that same task. The absolute volume change of estrogen in the bloodstream is greater when supplementing compared to suppressing, and they also work on different estrogens. Estrogen supplementation in postmenopausal females typically involves increasing estradiol, whereas estrogen suppression in postmenopausal women typically involves suppressing estrone, as it is the most prevalent, yet less powerful, estrogen in postmenopausal women. Thus, the effect of supplementation and suppression are likely quite different processes and may not affect neuropsychological performance in the same way. Additionally, we do not know enough about the action of estrone versus estradiol at the receptor site to determine how they will be used. More studies are needed to link estrogens and the distribution of estrogen receptors to neuropsychological performance.

There are several limitations to Studies 1 and 2. As mentioned, the studies did not directly test the working memory model. In addition, hormone levels were not assessed even though the measures have been shown to be sensitive to hormones (Grigorova et al., 2006; Hampson & Duff, 2001; Keenan et al., 2001). Most of the young women in the present study were on a long lasting contraceptive (e.g., depo-provara) and without hormone assays we cannot determine whether the sex effects were due to sex-related differences or hormone supplementation. The studies are also limited by age. Because only young university students took part in the Studies 1 and 2, it is unknown whether the results generalize to healthy middle-age and older adults. Finally, there was some indication that presenting tasks on the computer may have affected the sex-related differences. Anecdotally, males approached the n-back task more competitively than females, and the effect size for the female advantage on the object-location working memory task was weaker for the computer version. Future studies may employ

computer use questionnaires or test differences experimentally to help explain sex-related differences in the approach to computerized tasks.

There are several limitations to Study 3 and the research in general, some of which has already been discussed. It was difficult to recruit participants for the cancer control group, because the pool of participants within the study region who met criteria for the study was small. Without a cancer control group, it is uncertain whether the observed effects are due to estrogen suppression as opposed to the disease process. Furthermore, we did not have a baseline measure of cognitive functioning as initially planned. Women undergoing endocrine therapy serving as their own controls may help eliminate some of the potential confounds associated with cross-sectional studies. Premenopausal women were also not included in the study due to difficulty with recruitment; it is possible that premenopausal women would demonstrate more pronounced cognitive effects compared to postmenopausal women, as total estrogen depletion from the medications would be greater in premenopausal women. It is possible that estrone and estradiol target cognition differently, and that the suppression of estrone is most adverse for processing speed. Again, it would be interesting to develop a neuropsychological profile for the different estrogens. Regarding clinical relevance, the results of Study 3 may be reassuring for women undergoing endocrine therapy, as the differences are small and do not appear to affect memory, but rather generative thinking and processing speed.

In sum, this body of work, investigating the effects of sex and endocrine therapy on working memory and other neuropsychological functions, found some expected, and some unexpected, results. This pattern of results demonstrates that our knowledge of sex-related differences and endocrine therapy is evolving and there is much potential for fruitful research in this area. Several avenues of future research regarding sex, hormones, and neurocognition have already been suggested throughout this document, and include examining differences in strategy

use on various neurocognitive measures, examining the complex interplay of hormones, neurotransmitters, and genetics on neurocognition, examining the dose-response relationship of endocrine therapy on cognition, and examining the interplay among hormones and aging in women who have taken or are currently undergoing endocrine therapy. Studies such as these will lead to a greater understanding of this complex area and in turn, generate new areas of investigation.

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Appendix A: Consent form for Studies 1 and 2

Consent Form for "Manual and Computer Working Memory"

Researcher: Lisa Lejbak, Department of Psychology, U of S (phone: 966-2528; email: lisa.lejbak@usask.ca)
Supervisor: Dr. Vrbancic, Department of Clinical Health Psychology, Royal University Hospital (655-2347) and Dr. Crossley, Department of Psychology, University of Saskatchewan (966-5925)

Objective, Rationale, and Procedure: This experiment will investigate individual differences in object-location working memory across manual and computer tasks. Individual differences have been observed in verbal working memory but have not been investigated in object-location working memory, and it is uncertain whether these differences occur across manual and computerized tasks. You will be asked to complete a brief demographic questionnaire, a series of computer-based working memory tasks, and some other brief pencil-and-paper cognitive tasks. This experiment will not take longer than 70 minutes to complete and you will receive two credits for your participation, which are counted toward your psychology course.

Possible Risks: There are no known or foreseeable risks associated with this study.

Benefits to Participants: This experiment will provide participants with the opportunity to learn more about neuropsychological experiments, and more specifically about working memory. In addition, participants will receive 2 credits for their participation, which counts toward their final grade. Participants will also be able to request that a final document be sent to them so they may learn the results of the study. It should be noted, however, that the benefits of participation in this study are not guaranteed.

Freedom to Withdraw: You are free to withdraw from the study at any time without penalty. Withdrawal from the study at any point will not affect your academic status or affect your grade in your psychology course. If you decide to withdraw, your data will be deleted from the study and destroyed.

Confidentiality: There will be no personal identity information attached to your data. The consent form, which has your name on it, is kept separately from your data so no one, including the researcher, will know individual results from the experiments. All forms and data are stored in a locked cabinet in Dr. Crossley's clinic at the U of S for a minimum of five years, after which it will be destroyed. The only people that will have access to this information in the interim are the researcher and her supervisors, Drs. Vrbancic and Crossley.

Dissemination of Data: Data from this study will be presented only in aggregate form (i.e., individual results will not be presented). The results may be presented as part of a PhD dissertation, in research seminars, scientific conferences, and scientific papers.

Questions: If you have any questions concerning the study, please feel free to ask at any point; you are also free to contact the researchers at the numbers provided above if you have questions at a later time. This study has been approved on ethical grounds by the University of Saskatchewan Behavioural Sciences Research Ethics Board on January 28, 2004. Any questions regarding your rights as a participant may be addressed to that committee through the Office of Research Services (966-2084). Out of town participants may call collect. If you wish to know the results of this research, you may leave your contact information with the researcher or contact the researcher using the information at the top of the page.

Consent to Participate: I have read and understood the description provided above; I have been provided with an opportunity to ask questions and my questions have been answered satisfactorily. I consent to participate in the study described above, understanding that I may withdraw this consent at any time without academic penalty. I understand that although data from this study may be published, only aggregate data will be used and that my identity will be kept confidential. A copy of this consent form has been given to me for my records.

_____ _____

(Signature) (Date)

_____

(Researcher)

If you have any questions or concerns about this experiment or your rights as a participant, please contact the Office of Research Services at 306-966-2084

Appendix B: Debriefing Form for Studies 1 and 2

Thank you for participating in this study!

The present experiment was designed to test sex-related differences in working memory across manual and computer tasks. Sex-related differences in certain cognitive tasks are well documented. For example, males typically demonstrate an advantage on certain tests of spatial ability whereas females demonstrate an advantage on certain tests of verbal ability. Recently, Duff and Hampson (2001) documented a large female advantage on a test of working memory. This study was designed to extend their findings by determining whether the female advantage for working memory exists across domains (e.g., verbal, spatial, etc.), and across manual and computer tasks.

You completed a series of working memory tasks manually (the concentration task) and on the computer (i.e., the concentration task and the n-back task). These were the experimental tasks of interest. You also completed a series of pencil and paper tasks, which were the control tasks. The hypotheses are that the female advantage for working memory would occur regardless of task (i.e., concentration or n-back), domain (i.e., verbal, non-verbal, or object-location), or presentation (i.e., manual or computerized).

Your data is confidential and will be kept in a secure location. No personally identifying information is attached to your data. Results will be presented in aggregate form. If you wish to know the results of the study, you may leave your name with the researcher or contact the researcher in the near future.

If you have any questions or concerns about the present experiment, please contact Lisa Lejbak (phone: 966-2528; email: lisa.lejbak@usask.ca), Dr. Vrbancic (955-2347), or Dr. Crossley (966-5923). Alternatively, you can contact the Head of the Department of Psychology at 966-6701 or the Office of Research Services at 966-2084.

Thanks again for participating in the study!

Appendix C: Demographic Questionnaire for Studies 1 and 2

Participant number _____

The following is a brief demographic questionnaire deigned to elicit information that may be important to the current study. If you are not sure of an answer to a question or do not wish to answer a question, please leave the question blank. This questionnaire is anonymous and all answers will be kept confidential.

1. What is your age?

2. What year are you in at University?

3. What is your major?

4. What is your first language? If not English, are you fluent in English?

5. Please list any medications you are currently taking (please include birth control)

6. What is your dominant hand (i.e., with which hand do you MAINLY write, throw a ball, eat, etc.)?

7. Have you ever had a brain-related insult (e.g., seizure, stroke, concussion, etc.) or neurological disorder (e.g., multiple sclerosis)? If so, please explain.

8. Have you ever been diagnosed with a hormone disorder? If so, which one?

9. Have you ever been diagnosed with a psychiatric diagnosis? If so, which one?

Thank you for your contribution!

Appendix D: Recruitment Handout for Oncologists to Recruit Women Initiating Hormone Treatment

My name is Lisa Lejbak and I am a PhD student in psychology who is conducting a study into whether breast cancer drugs affect memory. Women often talk about memory changes but there aren't very many studies in this area. Knowing more will help women make decisions about care and cope with the changes.

I am looking for women who are taking tamoxifen or anastrozole as part of breast cancer treatment to take part in my study. Volunteers should be between the ages of 40 and 80 who have early stage breast cancer. This study will help us understand whether breast cancer drugs affect memory.

If you decide to take part, I will assess your memory twice. Each memory assessment will take two hours. An example of a memory task is having to remember details from a story. If need be, I can travel to your community if you aren't able to travel to Saskatoon or Regina.

Please contact me if you would like to take part in my study. You can email me at lisa.lejbak@usask.ca or phone collect (306) 227-5461. Messages are kept confidential.

Sincerely, Lisa Lejbak (PhD student), Department of Psychology

Research Ethics Board Approval Number: 05-243. This project was reviewed and approved by the University of Saskatchewan Behavioral Research Ethics Board in January 2006. If you want to know more about this process or if you have any questions about your right as a research participant, please contact Curtis Chapman, Ethics Officer, at (306)-966-2084 (collect). This study also has the support of the Saskatchewan Cancer Agency.

Appendix E: Recruitment Handout for Oncologists to Recruit Women Undergoing Cancer Treatment

My name is Lisa Lejbak and I am a PhD student in psychology who is conducting a study into whether breast cancer medications or cancer treatments affect memory. Women often talk about memory with medication changes but there aren't very many studies in this area. Knowing more will help women make decisions about care and cope with the changes.

I am looking for women who are taking tamoxifen or anastrozole as part of breast cancer treatment to take part in my study. I am also looking for women who have other kinds of cancer but are not taking those medications. Volunteers should be between the ages of 40 and 80 who have early stage breast cancer. This study will help us understand whether breast cancer drugs affect memory.

If you decide to take part, I will assess your memory once. The assessment will take two hours. An example of a memory task is having to remember details from a story. If need be, I can travel to your community if you aren't able to travel to Saskatoon or Regina.

Please contact me if you would like to take part in my study. You can email me at lisa.lejbak@usask.ca or phone collect (306) 227-5461. Messages are kept confidential.

Sincerely, Lisa Lejbak (PhD student), Department of Psychology

Research Ethics Board Approval Number: 05-243. This project was reviewed and approved by the University of Saskatchewan Behavioral Research Ethics Board in January 2006. If you want to know more about this process or if you have any questions about your right as a research participant, please contact Curtis Chapman, Ethics Officer, at (306)-966-2084 (collect). This study also has the support of the Saskatchewan Cancer Agency.

Appendix F: Recruitment Letter Sent by the Saskatchewan Cancer Agency Registry for Participants Undergoing Hormone Treatment

Hello,

My name is Lisa Lejbak and I am a PhD psychology student who is conducting a study into whether breast cancer medications affect memory. Women often say that their memory changes when they take breast cancer drugs, but there aren't very many studies that look at these changes. Knowing more about them will help women make choices about care and cope with any changes.

I am seeking women who are taking breast cancer medication (tamoxifen or anastrozole) as part of their treatment to take part in my study. I am looking for women who have had Stage 0 or Stage I breast cancer. Women who want to take part should not have a history of hormone disorder or brain injury. This is necessary because it is sometimes hard to separate past problems from the current effects of the drugs.

If you decide to take part, I will assess your memory once. The assessment will take two hours. The assessment will involve activities like remembering a story. If need be, I am able to travel to your community if you cannot travel to Saskatoon or Regina for the study.

This project was reviewed and approved by the University of Saskatchewan Behavioral Research Ethics Board in January 2006. If you want to know more about this process or if you have any questions about your rights as a research participant, please contact Curtis Chapman, Ethics Officer, at (306)-966-2084 (collect).

You have been identified as a potential participant for his study through the Registry at the Saskatchewan Cancer Agency. The Saskatchewan Cancer Agency (SCA) operates the Saskatoon Cancer Centre, the Allan Blair Cancer Centre in Regina, two cancer patient lodges, the Screening Program for Breast Cancer, and other cancer-related programs and services in the province. The SCA is authorized by legislation to keep a registry of all Saskatchewan residents who have been diagnosed with cancer, whether they are treated at an SCA cancer centre or by other areas of the health care system.

Every effort has been made to ensure that this letter does not reach families of women who have passed away. If a grieving family member receives this letter, please accept our heartfelt condolences and sincere apologies.

Please call or email me if you would like to take part in this study. **You can call (collect if necessary) 306-227-5461 or email lisa.lejbak@usask.ca.** Your messages will be kept confidential. If you prefer not to get letters about participating in a study again, please call Karen Robb from the Saskatchewan Cancer Agency at (306)-766-2973. We will then make sure that your name is taken off research mailing lists.

Thank you for your time.

Sincerely,

Lisa Lejbak, PhD Student
Department of Psychology, University of Saskatchewan
306-374-3835 or (306)-227-5461; lisa.lejbak@usask.ca
Research Ethics Board Approval Number: 05-243

Appendix G: Recruitment Letter sent by the Saskatchewan Cancer Agency Registry to Recruit the Cancer Control Group

Hello,

My name is Lisa Lejbak and I am a PhD psychology student who is conducting a study into whether cancer treatments affect memory and other brain functions. I am looking for women who have had early stage cancer (any type) to participate in a study to see how their memory compares to women who are taking breast cancer hormonal medications.

Women with estrogen-sensitive breast cancer often say that their memory changes when they take breast cancer hormonal medications, but there aren't very many studies that look at these changes, and we don't know whether these changes are any different than women who have undergone cancer treatment for other types of cancer. Knowing more about how cancer treatments affect memory will help women affected by early stage cancer make choices about care and cope with any changes.

I am seeking women who have undergone early stage cancer treatment. Women who want to take part should not have a history of hormone disorder or brain injury. This is necessary because it is sometimes hard to separate past problems from the current effects of cancer treatment.

If you decide to take part, I will assess your memory once. The assessment will take two hours at the most. The assessment will involve activities like remembering a story. If need be, I am able to travel to your community if you cannot travel to Saskatoon.

This project was reviewed and approved by the University of Saskatchewan Behavioral Research Ethics Board in January 2006. If you want to know more about this process or if you have any questions about your rights as a research participant, please contact the U of S Ethics Officer at (306)-966-2084 (collect). This project also has the support of the Saskatchewan Cancer Agency and Saskatoon Cancer Centre.

Please call or email me if you would like to take part in this study. You can call 306-227-5461 or email lisa.lejbak@usask.ca. Your messages will be kept confidential.

Thank you for your time.

Sincerely,

Lisa Lejbak, PhD Student
Department of Psychology, University of Saskatchewan
(306)-227-5461 or (306)-374-3835; lisa.lejbak@usask.ca
Research Ethics Board Approval Number: 05-243

Appendix H: Recruitment Letter Sent to Participants through the Saskatoon Council on Aging for Control Group and Cancer Group

Hello,

I am a PhD psychology student studying the effects of normal aging and cancer treatments on memory. I am looking for 2 groups of women to participate in this study:

1. Relatively healthy woman (i.e., no history of cancer)
2. Women who have been treated for early stage cancer of any kind (with the exception of skin and central nervous system cancer).

For healthy women, you should be between the ages of 40 and 60).

For women who have been treated for cancer, you should be between the ages of 40 and 80**,** and have been treated for an early stage cancer (i.e., cancer that has not spread). The treatment should have occurred between 1 and 5 years ago. You should not have had chemotherapy as part of your treatment, but surgery, radiation, and/or medication treatments are okay.

You should not have a history of a brain disorder (e.g., stroke, dementia) because it is sometimes hard to separate past problems from current functioning.

Please feel free to pass this letter on to other women who may be interested (e.g., friends or family members) if you do not qualify for this study.

The study will take no more than two hours of your time and will involve activities like having to remember a list of words, as well as some questionnaires. Assessments can take place either in your home or at Royal University Hospital.

You have been identified as a potential participant through the Saskatoon Council on Aging's database, which has approved this study. You are free to choose whether to participate in this study, and are free to withdraw from the study at any point if you decide to participate. Please contact June Gawdun (306-652-2255) if you have any questions or concerns about the Saskatoon Council on Aging.

This project was reviewed and approved by the University of Saskatchewan Behavioral Research Ethics Board in January 2006. If you want to know more about this process or if you have any questions about your rights as a research participant, please contact the U of S Ethics Officer at (306)-966-2084 (collect).

Please call or email me (Lisa Lejbak) if you would like to take part in this study. You may call **306-227-5461** or **306-655-2355**; or email **lisa.lejbak@usask.ca**. Messages will be kept confidential.

Thank you for your time. Sincerely,

Lisa Lejbak, PhD Student
Department of Psychology, University of Saskatchewan
(306)-227-5461 or (306)-655-2355; lisa.lejbak@usask.ca
Research Ethics Board Approval Number: 05-243

Appendix I: Consent Form for Women Initiating Hormone Treatment

Consent Form for "The Effects of Menopause and Anti-Estrogen Medications on Memory Functions"

Researcher: Lisa Lejbak, Department of Psychology, U of S (phone: 966-2528; email: lisa.lejbak@usask.ca)

Supervisors: Dr. Vrbancic, Department of Clinical Health Psychology, Royal University Hospital (655-2347) and Dr. Crossley, Department of Psychology, University of Saskatchewan (966-5925)

Objective, rationale and procedure: We would like to know if drugs that decrease estrogen (e.g., tamoxifen and anastrozole) affect memory in women with breast cancer. Women who take these drugs often mention memory problems but this area has not been looked at thoroughly.

Your memory will be assessed twice, once before you begin taking the drug (or within the first week of starting) and then four months later. Each time, you will be asked to fill out a brief questionnaire about yourself and perform memory tasks (e.g., remembering a story). You will also be asked to perform some language and attention tasks (e.g., naming objects). Finally, you will be asked to fill out questions about your psychological health (e.g., questions about anxiety). Each assessment will take about 2 hours. You may take breaks if you like.

Women who want to take part should not have a history of a hormone disorder or brain injury. This is necessary because sometimes it is difficult to separate past problems from the current effects of the drugs. If this applies to you, please tell the experimenter that you prefer not to participate in the study. You do not need to explain in detail, and this information will be kept in confidence. Your decision to take part or not to take part in this study will not affect the health services provided to you now or in the future.

Possible risks: There are no known or anticipatable risks associated with this study other than mental fatigue.

Benefits to participants: You will have a chance to learn more about neuropsychological (i.e., "memory") research and brain functioning. You can ask for a copy of the final results if you like. You will be given feedback on your individual performance if you ask for it. The benefits of participation in this study are not guaranteed.

Freedom to withdraw: You are free to withdraw from the study at any time without penalty and without having to explain the reason to the researcher. If you decide to withdraw, your data will be removed from the study and destroyed. Please know that your decision to participate or not to participate in this study will in no way affect the health services provided to you now or in the future.

Confidentiality: There will not be any personal identification attached to your data. We will not be able to link your performance with you. This consent form, which has your name on it, is kept separately from your data. All forms and data are stored in a locked cabinet in Dr. Vrbancic's office at Royal University Hospital for a minimum of five years, after which they will be destroyed. The only people that will have access to this information as the study is ongoing are the researcher, Lisa Lejbak, and her supervisors, Dr. Vrbancic and Dr. Crossley.

Dissemination of data: The results from this study will only be discussed in group form (i.e., individual results will not be presented in papers or at conferences). The results will be presented as part of a PhD dissertation, in research lectures, scientific conferences, and scientific papers. The results will also be shared with the oncologists at the Saskatchewan Cancer Agency.

Questions: Please feel free to ask questions at any point during the study. You are also welcome to call or email the researcher if you have questions later on. This study has been approved on ethical grounds by the University of Saskatchewan Behavioural Sciences Research Ethics Board on October 11, 2005. Any questions about your rights as a participant may be addressed to that committee through the Office of Research Services (966-2084). Out of town participants may call collect. If you would like to receive information about the results of the study, please leave your contact information with the researcher or contact the researcher later on.

Consent to participate: I have read and understood the description provided above. I have been provided with an opportunity to ask questions and my questions have been answered satisfactorily. I consent to participate in the study described above, understanding that I may withdraw this consent at any time without explanation or repercussions. I understand that although data from this study may be published, only group data will be used and that my identity will be kept confidential. A copy of this consent form has been given to me for my records.

_____ _____

(Signature) (Date)

_____

(Researcher)

If you have any questions or concerns about this experiment or your rights as a participant, please contact the Office of Research Services at 306-966-2084.

Appendix J: Consent Form for Control Group and Women Already Undergoing HormoneTherapy

Consent Form for "The Effects of Menopause and Anti-Estrogen Medications on Memory Functions"

Researcher: Lisa Lejbak, Department of Psychology, U of S (phone: 966-2528; email: lisa.lejbak@usask.ca)

Supervisors: Dr. Vrbancic, Department of Clinical Health Psychology, Royal University Hospital (655-2347) and Dr. Crossley, Department of Psychology, University of Saskatchewan (966-5925)

Objective, rationale and procedure: We would like to know if drugs that decrease estrogen (e.g., tamoxifen and anastrozole) affect memory in women with breast cancer. Women who take these drugs often mention memory problems but this area has not been looked at thoroughly.

Your memory will be assessed once. You will be asked to fill out a brief questionnaire about yourself and perform memory tasks (e.g., remembering a story). You will also be asked to perform some language and attention tasks (e.g., naming objects). Finally, you will be asked to fill out questions about your psychological health (e.g., questions about anxiety). Each assessment will take about 2 hours. You may take breaks if you like.

Women who want to take part should not have a history of a hormone disorder or brain injury. This is necessary because sometimes it is difficult to separate past problems from the current effects of the drugs. If this applies to you, please tell the experimenter that you prefer not to participate in the study. You do not need to explain in detail, and this information will be kept in confidence. Your decision to take part or not to take part in this study will not affect the health services provided to you now or in the future.

Possible risks: There are no known or anticipatable risks associated with this study other than mental fatigue.

Benefits to participants: You will have a chance to learn more about neuropsychological (i.e., "memory") research and brain functioning. You can ask for a copy of the final results if you like. You will be given feedback on your individual performance if you ask for it. The benefits of participation in this study are not guaranteed.

Freedom to withdraw: You are free to withdraw from the study at any time without penalty and without having to explain the reason to the researcher. If you decide to withdraw, your data will be removed from the study and destroyed. Please know that your decision to participate or not to participate in this study will in no way affect the health services provided to you now or in the future.

Confidentiality: There will not be any personal identification attached to your data. We will not be able to link your performance with you. This consent form, which has your name on it, is kept separately from your data. All forms and data are stored in a locked cabinet in Dr. Vrbancic's office at Royal University Hospital for a minimum of five years, after which they will be destroyed. The only people that will have access to this information as the study is ongoing are the researcher, Lisa Lejbak, and her supervisors, Dr. Vrbancic and Dr. Crossley.

Dissemination of data: The results from this study will only be discussed in group form (i.e., individual results will not be presented in papers or at conferences). The results will be presented as part of a PhD dissertation, in research lectures, scientific conferences, and scientific papers. The results will also be shared with the oncologists at the Saskatchewan Cancer Agency.

Questions: Please feel free to ask questions at any point during the study. You are also welcome to call or email the researcher if you have questions later on. This study has been approved on ethical grounds by the University of Saskatchewan Behavioural Sciences Research Ethics Board on October 11, 2005. Any questions about your rights as a participant may be addressed to that committee through the Office of Research Services (966-2084). Out of town participants may call collect. If you would like to receive information about the results of the study, please leave your contact information with the researcher or contact the researcher later on.

Consent to participate: I have read and understood the description provided above. I have been provided with an opportunity to ask questions and my questions have been answered satisfactorily. I consent to participate in the study described above, understanding that I may withdraw this consent at any time without explanation or repercussions. I understand that although data from this study may be published, only group data will be used and that my identity will be kept confidential. A copy of this consent form has been given to me for my records.

_____ _____

(Signature) (Date)

_____

(Researcher)

If you have any questions or concerns about this experiment or your rights as a participant, please contact the Office

Appendix K: Debriefing Form for All Participants in Study 3

Debriefing Form for "Cancer Treatments, Hormones, and Memory"

Thank you for participating in this study!

The present experiment was designed to assess memory and higher brain functions in women who are either experiencing menopausal symptoms, are being treated with anti-estrogens for breast cancer treatment, or have received treatment for early stage cancer. Memory has been shown to be sensitive to estrogen levels- for example, Hampson and Duff (2000) found that women taking hormone replacement therapy performed better than women not taking hormone replacement therapy on a variety of working memory measures. Women taking medications that suppress estrogen (e.g., tamoxifen and anastrozole) often report that their memory and attention declines; however, there are few human studies that have assessed whether the effects are any worse than women undergoing menopause or women undergoing non-hormonal cancer treatment.

You completed a series of memory and other higher brain functions tasks. Our hypotheses are that women taking anti-estrogens as part of breast cancer treatment would perform poorer on measures of working memory as compared to women undergoing natural menopause and non-hormonal cancer treatment, and that memory would decline over the four months in women who were just beginning anti-estrogen treatment at the first assessment.

Your data is confidential and will be kept in a secure location. No personally identifying information is attached to your data. Results will be presented in aggregate form. If you wish to know the results of the study, you may leave your name with the researcher or contact the researcher in the near future.

If you have any questions or concerns about the present experiment, please contact Lisa Lejbak (phone: 227-5461 or email: lisa.lejbak@usask.ca) or Dr. Vrbancic (955-2347) and Dr. Crossley (966-5925). Alternatively, you can contact the Head of the Department of Psychology at 966-6701 or the Office of Research Services at 966-2084.

Thanks again for participating in the study!

Appendix L: Demographic and Health Questionnaire for Study 3

Demographic and Health Questionnaire Participant Number_____

The following is a brief demographic questionnaire deigned to elicit information that may be important to the study. If you are not sure of an answer to a question or do not wish to answer a question, please leave the question blank. This questionnaire is anonymous and all answers will be kept confidential.

1. What is the date of your birth (Day/Month/Year)?

2. Is your vision corrected to normal (i.e., are you wearing the glasses you have been prescribed)?

3. Is your hearing corrected to normal?

4. What is your first language? If it is not English, are you fluent in English?

5. Have you been diagnosed with cancer? (If the answer is "no" please skip to question 11)?

6. What type of cancer has been diagnosed?

7. What stage of cancer was diagnosed? (0, 1, 2, 3, or 4)

8. Approximately what was the date of your breast cancer diagnosis (Day/Month/Year)?

9. What treatment have you received for breast cancer (e.g., surgery, radiation therapy)? On which date(s) did you receive the treatment?

10. Are you currently taking hormone treatment for breast cancer (e.g., tamoxifen or anastrozole)? If so, what is the dose?

11. Are you still menstruating? Are you pre-menopausal, peri-menopausal, or post-menopausal (no periods for over one year)? If still menstruating, what is the date of your last regular menstrual cycle?

12. Please list any medications you are currently taking:

13. Have you taken hormone replacement therapy in the past?

14. What is your dominant hand (i.e., with which hand do you MAINLY write, throw a ball, eat, etc.)?

15. Have you ever had any kind of brain injury (e.g., seizure, stroke, concussion, etc.)? If so, please state the diagnosis and whether it is currently active.

16. Have you ever been diagnosed with a hormone disorder? If so, please state the diagnosis and whether it is currently active.

17. Have you ever been diagnosed with a psychiatric disorder (e.g., depression, schizophrenia)? If so, please state the diagnosis and whether it is currently active.

18. Please provide your height and weight if you wish.

Thank you for your contribution!

Appendix M: Menopause Symptom Questionnaire

MENOPAUSE QUESTIONNAIRE: SYMPTOM ANALYSIS
Please indicate how bothered you are **now and in the past month** by any of the following:

	Not at all	**A little bit**	**Moderately**	**Quite a bit**	**Extremely**
I have hot flashes	1	2	3	4	5
I have night sweats	1	2	3	4	5
I have difficulty getting to sleep	1	2	3	4	5
I have difficulty staying asleep I get heart palpitations or a sense of butterflies in my chest or stomach	1	2	3	4	5
I feel like my skin is crawling	1	2	3	4	5
I feel more tired than usual	1	2	3	4	5
I have difficulty concentrating	1	2	3	4	5
My memory is poor	1	2	3	4	5
I am more irritable than usual	1	2	3	4	5
I feel more anxious than usual	1	2	3	4	5
I have more depressed moods	1	2	3	4	5
I am having mood swings	1	2	3	4	5
I have crying spells	1	2	3	4	5
I have headaches	1	2	3	4	5
I have pain or burning when urinating	1	2	3	4	5
I have bladder infections	1	2	3	4	5
I have uncontrollable loss of stool or gas	1	2	3	4	5
My vagina is dry	1	2	3	4	5
I have vaginal itching	1	2	3	4	5
I have an abnormal vaginal discharge	1	2	3	4	5
I have vaginal infections	1	2	3	4	5
I have pain with entry during	1	2	3	4	5

intercourse

	Not at all	A little bit	Moderately	Quite a bit	Extremely
I have abdominal pain during intercourse	1	2	3	4	5
I have bleeding after intercourse	1	2	3	4	5
I lack desire or interest in sexual activity	1	2	3	4	5
I have difficulty achieving orgasm	1	2	3	4	5
My stomach feels like it's Bloated or I've gained weight	1	2	3	4	5
I have breast tenderness	1	2	3	4	5
I have muscle/joint pains	1	2	3	4	5
I have numbness	1	2	3	4	5
I have panic attacks	1	2	3	4	5

Other:

Appendix N: Neurotoxicity Measure

Neurotoxicity Symptom Checklist

The following is a list of problems that people sometimes have. Please read each item carefully and circle the number that best describes how much the problem has distressed or bothered you in the past 7 days including today. Circle only one number for each problem and do not skip any items.

	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Feeling tired	1	2	3	4	5
2. Headaches	1	2	3	4	5
3. Diarrhea	1	2	3	4	5
4. Feeling confused	1	2	3	4	5
5. Lack of coordination	1	2	3	4	5
6. Perspiring for no reason	1	2	3	4	5
7. Unexplained weight loss	1	2	3	4	5
8. Indigestion	1	2	3	4	5
9. Excessive salivation	1	2	3	4	5
10. Tightness in chest	1	2	3	4	5
11. Trembling in hands	1	2	3	4	5
12. Muscle twitching	1	2	3	4	5
13. Difficulty buttoning clothes	1	2	3	4	5
14. Loss of balance	1	2	3	4	5
15. Blurred vision	1	2	3	4	5
16. Slurred speech	1	2	3	4	5
17. Skin rashes	1	2	3	4	5
18. Hearing difficulties	1	2	3	4	5
19. Problems with smell or taste	1	2	3	4	5

Appendix O: Object Location Memory Task Instructions (all studies)

We are interested in seeing how well you can find and remember the positions of the shapes and objects within an array.

In front of you there is a 4 x 5 array. Hidden within this array there are 10 pairs of (objects, shapes, or novel shapes). These are the ten (objects, shapes, or novel shapes) here (**point to velcro pad next to the array which displays the 10 objects, shapes, or novel shapes**). Do they all look different to you? There are **two** of each of these (objects, shapes, or novel shapes) colours hidden somewhere within the array (**point to each object, shape, or novel shape on the Velcro board**).

Your task is to search through all the flaps to find all 10 matching pairs. Now, when searching through the array, I want you to search by lifting (or clicking on) two flaps at a time *(*pantomine lifting two flaps simultaneously*)*. Every time you find a matching pair I want you to pause, and I will put the corresponding (object, shape, or novel shapes) on the board to show you that you have found it and do not need to keep looking for it *(*remove and replace a coloured dot on the Velcro board as a demonstration*)*.

Following that, I want you to lower the flaps (click on a new pair) and keep on searching. Your task will be finished when you have found all ten matching pairs, and therefore all ten (objects, shapes, novel shapes) are back up on the board.

Do you understand what you are supposed to do?

Now, I do time you on this task *(*show stopwatch*)* but time is not the most important thing. The most important thing is to find all ten pairs in as few choices as possible. In other words, lifting (or clicking) as few total flaps as possible.

Do you have any questions?

I am going to remove tokens from the pad here *(*start removing*)*. Remember, I will be putting them back as you find each pair. When you've finished, all ten (objects shapes, or novel shapes pairs) will be back on the pad, showing that you've found all ten matching pairs.

Go ahead whenever you're ready.

*(*Start timing when subject opens flaps. Record, in sequence, the numbers of the two locations chosen each time the flaps are opened. Once the subject has found all 10 atching pairs, stop the stopwatch and record the total time elapsed.*)*

Note: For the compouter version, participants were instructed to click on two flaps at a time. When they clicked on a third flap, the first two would close.

Appendix P: N-Back Instructions for Studies 1 and 2

You will see a series of letters one at a time. Each letter will be presented on the computer screen fairly quickly one after another.

For every letter that you see, decide if it is the same letter or a different letter from the letter you saw "2-letters ago". Pay attention to all of the letters, and once the third letter is shown, quickly decide whether you think the letter is the same or different from the letter you saw "2-letters back". Let's try an example.

(A-Y-a-Y-E are shown on the screen at a rate of 1 second).

You saw an 'A', then a 'Y', then an 'a', then a 'Y', and then an 'E'. Starting with the third letter, you would have responded "same" because the 'a' matched the letter 2-letters back ('A'). Note that upper and lower case letters are considered the same letter. You would also have responded "same" for the 'Y', because it matched the letter 2-letters back ('Y').
Finally, you would have responded "different" for the 'E', because it did not match the letter 2-letters back ('A').

When you respond, press the 'same' key for letters that match 2-back letters, and the "different" key for letters that do not match 2-back letters. After the first 2 letters appear, respond to every letter that you see. Please respond as quickly and as accurately as you can. We will start with practice trials.

(Two sets of practice trials are given)

Remember, begin responding to each letter after the first 2 letters appear. You are to say whether the letter on the screen is the same as the letter you saw "2-letters-back", or different from the letter you saw "2-letters-back". Please respond as quickly and accurately as you can.

Try to answer all of them. If you lose your place, start again from the current letter on the screen. Remember, do not differentiate between upper and lower case ('A' and 'a' are considered the same letter).

(note: the instructions for the location and object versions were the same but modified for the stimulus condition)

Appendix Q: N-Back Instructions for Study 3 (Hormone Therapy Study)

You will see a series of letters one at a time. Each letter will be presented on the computer screen fairly quickly, one after another. Decide whether the letter on the screen is the same as the last letter you saw. This is easiest to explain by showing you. Let's try an example. Decide whether the second letter you see is the same as the one right before it.

(An “A” followed by an “A” appears on the screen)

You first saw 'A', followed by 'A'. You would have pressed the white button to show that 'A' is the same as the 'A' on the screen before.

Let's try another example. Decide whether the letter on the screen is the same as the letter that came right before it.

(An “A” followed by an “E” appears on the screen)

You saw 'A', followed by 'E'. You would NOT have pressed the white button because 'A' is not the same as 'E'. Now let's try a longer example. Each time you see a new letter, decide whether it is the same as the letter that came immediately before it. Press the white button if it is the same. Do NOT respond if it is different.

(A-A-E-A appears on the screen).

You saw 'A', then 'A', then 'E', then 'A'. You would have pushed the button for your first response because 'A' is the same as 'A'. You would NOT have pushed the button for the second response because 'E' is not the same as the 'A' right before. And you would NOT have pushed the button because the 'A' is not the same as the 'E' before.

(Two sets of practice trials are given, with feedback)

Now we are going to try something a little more difficult. This time, instead of saying whether the letter is the same as the one immediately before, you will say whether the letter is the same as the letter TWO letters before. Here is an example. Say you saw 'a', then 'E', then 'A' then 'E' then 'E' Here is an example (a-E-A-E-E). You would start responding with the third letter. 'A' is the same as 'a', so you would push the white button. 'E' is the same as 'E' so you would push the white button. But 'E' is not the same as 'A' so you would not respond.

Let's try an example. (Example is shown). You saw 'A', then 'E', then 'A', then 'E', then 'o', then 'E' (A-E-A-E-o-E). Starting with the third letter, you would have responded 'same', 'same', 'no response', 'same'.
Let's practice. You are to push the white button if the letter is the same as what you saw 2-letters back, but do not respond if it is not the same. You will be told if your answer is 'correct or 'incorrect'.

(Two sets of practice trials are given, with feedback).

Good. Now we are going to try the same thing, only this time instead of seeing letters, you will see a circle move around on the screen. You are to say whether the circle is in the same location as the one right before it. Press the white button if it is the same. Let's see an example.

(Example of the circle moving in the same location is given).

You would have pressed the white button to indicate that the location is the same as the one you saw right before it. Let's try an example where the location is not the same.

(Example of the circle moving in a different location is given)

You would not have responded because the location is NOT the same as the location immediately before it. Let's practice. Press the white button if the location is the same as what you saw immediately before, but do not press the button if it is not the same. You will be told if your answer is 'correct or 'incorrect'.

Now we're going to try something more difficult. This time, you will need to say whether the location is the same as what you saw two locations back. Press the white key if it is the same, but do not respond if it is different.

(One set of practice trials are given, with feedback)

Your first response would have been "same", but the next was different, so you would not have responded. Are you ready for some practice trials?

(One set of practice trials are given, with feedback)

Location Condition:
For these next few, you will say whether the location you see is the same as two locations back. Press the white key if it is the same, but do not respond if it is not the same. You will not be told whether you are correct or incorrect. After the first 2 locations appear, respond to every location that you see. Try to answer them all, but if you lose your place, start again from the current location on the screen.

Letter Condition:
For these next few, you will say whether the letter is the same as two letters before. Press the white key if it is the same, but do not respond if it is different. You will not be told whether you are correct or incorrect. After the first 2 letters appear, respond to every letter that you see. Try to answer them all, but if you lose your place, start again from the current letter on the screen.